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Hajenius PJ, Mol F, Mol BWJ, Bossuyt PMM, Ankum WM, Van der Veen F

Hajenius PJ, Mol F, Mol BWJ, Bossuyt PMM, Ankum WM, Van der Veen F.
Interventions for tubal ectopic pregnancy.
Cochrane Database of Systematic Reviews 2007, Issue 1. Art. No.: CD000324.
DOI: 10.1002/14651858.CD000324.pub2.

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[Intervention Review]

Interventions for tubal ectopic pregnancy

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Editorial group: Cochrane Gynaecology and Fertility Group
Publication status and date: Edited (no change to conclusions), published in Issue 1, 2009.

Citation: Hajenius PJ, Mol F, Mol BWJ, Bossuyt PMM, Ankum WM, Van der Veen F. Interventions for tubal ectopic pregnancy. *Cochrane Database of Systematic Reviews* 2007, Issue 1. Art. No.: CD000324. DOI: 10.1002/14651858.CD000324.pub2.

ABSTRACT

Background

Treatment options for tubal ectopic pregnancy are; (1) surgery, e.g. salpingectomy or salpingo(s)tomy, either performed laparoscopically or by open surgery; (2) medical treatment, with a variety of drugs, that can be administered systemically and/or locally by various routes and (3) expectant management.

Objectives

To evaluate the effectiveness and safety of surgery, medical treatment and expectant management of tubal ectopic pregnancy in view of primary treatment success, tubal preservation and future fertility.

Search methods

We searched the Cochrane Menstrual Disorders and Subfertility Group's Specialised Register, Cochrane Controlled Trials Register (up to February 2006), Current Controlled Trials Register (up to October 2006), and MEDLINE (up to October 2006).

Selection criteria

Randomized controlled trials (RCTs) comparing treatments in women with tubal ectopic pregnancy.

Data collection and analysis

Two review authors independently extracted data and assessed quality. Differences were resolved by discussion with all review authors.

Main results

Thirty five studies have been analyzed on the treatment of tubal ectopic pregnancy, describing 25 different comparisons.

Surgery

Laparoscopic salpingostomy is significantly less successful than the open surgical approach in the elimination of tubal ectopic pregnancy (2 RCTs, n = 165, OR 0.28, 95% confidence interval (CI) 0.09 to 0.86) due to a significant higher persistent trophoblast rate in laparoscopic surgery (OR 3.5, 95% CI 1.1 to 11). However, the laparoscopic approach is significantly less costly than open surgery (P = 0.03). Long term

follow up (n = 127) shows no evidence of a difference in intra uterine pregnancy rate (OR 1.2, 95% CI 0.59 to 2.5) but there is a non significant tendency to a lower repeat ectopic pregnancy rate (OR 0.47, 95% 0.15 to 1.5).

Medical treatment
Systemic methotrexate in a fixed multiple dose intramuscular regimen has a non significant tendency to a higher treatment success than laparoscopic salpingostomy (1 RCT, n = 100, OR 1.8, 95% CI 0.73 to 4.6). No significant differences are found in long term follow up (n=74): intra uterine pregnancy (OR 0.82, 95% CI 0.32 to 2.1) and repeat ectopic pregnancy (OR 0.87, 95% CI 0.19 to 4.1).

Expectant management
Expectant management is significantly less successful than prostaglandin therapy (1 RCT, n = 23, OR 0.08, 95% CI 0.02 to 0.39).

Authors' conclusions

In the surgical treatment of tubal ectopic pregnancy laparoscopic surgery is a cost effective treatment. An alternative non surgical treatment option in selected patients is medical treatment with systemic methotrexate. Expectant management can not be adequately evaluated yet.

PLAIN LANGUAGE SUMMARY

Interventions for tubal ectopic pregnancy

Approximately 1% of fertilized eggs implant outside the uterine cavity and develop into extra uterine pregnancies known as ectopic pregnancies. Ectopic pregnancies can occur anywhere along the reproductive tract with the most common site being the fallopian tube.
An ectopic pregnancy in the fallopian tube, if not treated, can cause tubal rupture and/or intra abdominal bleeding. Treatment options for tubal ectopic pregnancy are surgery, medical treatment, and expectant management.
This review of 35 randomised controlled trials found that laparoscopic surgery is feasible and less expensive than open surgery in the treatment of tubal ectopic pregnancy. In selected patients, non-surgical treatment options can be used. Medical treatment with systemic methotrexate is an option for women with tubal ectopic pregnancy with no signs of bleeding whose pregnancy hormone blood levels are relatively low. An evaluation of expectant management of tubal ectopic pregnancy cannot be adequately made yet.

BACKGROUND

The diagnosis of ectopic pregnancy can be made by noninvasive methods, i.e. sensitive pregnancy tests (in urine and serum), and high resolution transvaginal sonography, which have been integrated in reliable diagnostic algorithms (Ankum 1993; Mol 1998b). These algorithms, in combination with the increased awareness and knowledge of risk factors among both clinicians and patients, have enabled an early and accurate diagnosis of ectopic pregnancy. Probabilistic models including the pre-test probability of the patient determined from medical history, as well as physical-, ultrasound- and laboratory findings (serum human chorionic gonadotropin (hCG) and progesterone levels) have improved the management of ectopic pregnancy, especially in women who have a pregnancy of unknown location (PUL) (Ankum 1995; Mol 1999b; Banerjee 2001; Condous 2004; Condous 2005). As a consequence, the clinical presentation of ectopic pregnancy has changed from a life threatening disease necessitating emergency surgery to a more benign condition in sometimes even asymptomatic patients. This in turn has resulted in major changes in the options available for therapeutic management.

For tubal ectopic pregnancy therapeutic intervention is now possible before the patient's condition has deteriorated and before tubal integrity is lost, thereby improving clinical outcome and reducing costs associated with emergency surgery. Furthermore, advances in laparoscopic surgery have enabled a laparoscopic approach in the majority of patients with tubal ectopic pregnancy (Sultana 1992).
Salpingo(s)tomy has become an option in patients desiring future fertility. Compared to salpingectomy, salpingo(s)tomy aims to save tubal integrity to maintain reproductive capacity. A well recognized hazard of a salpingo(s)tomy is incomplete removal of trophoblastic tissue, resulting in rising or plateauing serum hCG concentrations postoperatively (persistent trophoblast), which may lead to recurrence of clinical symptoms (Seifer 1990). To detect persistent trophoblast, postoperative serum hCG monitoring is mandatory (Hajenius 1995a; Spandorfer 1997).

Nonsurgical strategies, i.e. medical treatment and expectant management, have become a focus of research as laparoscopy is no longer needed for the diagnosis of tubal ectopic pregnancy. Selecting the subset of tubal ectopic pregnancies amenable for these strategies without putting the patient at risk is of the utmost importance (Tulandi 1991b; Hochner 1992; Maymon 1996).

Systemic and local administration of drugs have been introduced in selected patients with an unruptured tubal ectopic pregnancy without active bleeding. Selection criteria used are; the size of the tubal ectopic pregnancy, maximum serum hCG concentrations, and fetal cardiac activity. The most commonly used drug in clinical practice is methotrexate. Methotrexate is a folic acid antagonist which inhibits de novo synthesis of purines and pyrimidines, thereby interfering with DNA synthesis and cell proliferation. Secondary to its effect on highly proliferative tissues, methotrexate has a strong dose related potential for toxicity. Side effects include stomatitis, conjunctivitis, gastritis-enteritis, impaired liver function, bone marrow depression, and photosensitivity. When methotrexate is given systemically, it can be given in a fixed *multiple dose* intramuscular regimen or in a *variable dose* intramuscular regimen.

The fixed multiple dose regimen is derived from the treatment of gestational trophoblastic disease described by Bagshawe 1989 and Goldstein 1976. This regimen is combined with folinic acid (citrovorum/leucovorin rescue) to reduce chemotherapy toxicity. The regimen of Bagshawe comprises a total of four injections of methotrexate 50 mg intramuscularly alternated with folinic acid 6 mg intramuscularly 30 hours after each methotrexate injection with a rest period of six days. The therapeutic protocol of Goldstein comprises a total of four injections of methotrexate 1 mg/kg intramuscularly alternated with folinic acid 0.1 mg/kg intramuscularly 24 hours after each methotrexate injection. This regimen was first used to treat a patient with an interstitial pregnancy (Tanaka 1982). The first report for a tubal ectopic pregnancy was in a patient with severe ovarian hyperstimulation syndrome, and surgery was therefore contraindicated (Chotiner 1985). The first case series of six patients was described by Ory 1986.
In 1989, Stovall individualized the methotrexate dosage to improve patient compliance, to minimize side effects, and to reduce overall costs, which ultimately led to a single dose regimen of 50 mg/m^2 body surface area given intramuscularly without folinic acid (Stovall 1991; Stovall 1993).
Other efforts to attain maximal efficacy while minimizing or eliminating adverse effects resulted in various protocols for local medical treatment administered into the gestational sac transvaginally under sonographic or under laparoscopic guidance. Drugs that have been used for local treatment are methotrexate (Pansky 1989; Fernandez 1993), prostaglandins (Lindblom 1987; Egarter 1988), and hyperosmolar glucose (Lang 1989).
To evaluate treatment response after medical treatment, close serum hCG monitoring is mandatory to detect impending treatment failure and inadequately declining serum hCG concentrations. Serum hCG clearance curves after systemic methotrexate treatment are available (Hajenius 1997; Saraj 1998; Natale 2004).

In 1955, Lund was the first to practice expectant management in patients suspected of having an ectopic pregnancy who were not distressed on admission (Lund 1955). Expectant management has been advocated, based on the knowledge that the natural course of many early ectopic pregnancies is a self limiting process, ultimately resulting in tubal abortion or reabsorption (Mashiach 1982). Since the work of these pioneers, only a few studies have been published describing expectant management in selected patients with small ectopic pregnancies without fetal cardiac activity, an upper limit for serum hCG concentration that continues to decline and/or a low serum progesterone concentration (Korhonen 1994; Hajenius 1995b; Elson 2004). Close serum hCG monitoring is mandatory to detect inadequately declining serum hCG concentrations. Clear criteria for therapeutic intervention have not been defined yet. One study described serum hCG dynamics during spontaneous resolution of ectopic pregnancy (Korhonen 1994).

In summary, many treatment options are now available to the clinician in the treatment of tubal ectopic pregnancy:

- surgery, e.g. salpingectomy or salpingo(s)tomy, either performed laparoscopically or by open surgery
- medical treatment, with a variety of drugs, that can be administered systemically or locally or both by various routes (transvaginally under sonographic guidance or under laparoscopic guidance)

- expectant management.

OBJECTIVES

To evaluate the effectiveness and safety of surgery, medical treatment and expectant management of tubal ectopic pregnancy in view of primary treatment success, tubal preservation and future fertility.

METHODS

Criteria for considering studies for this review

Types of studies

Only randomised controlled trials were considered which compared one treatment with another in the management of tubal ectopic pregnancy and where the allocation to either treatment was created by random allocation. Non randomised controlled trials were excluded.

Types of participants

Women with a diagnosis of tubal ectopic pregnancy.

Types of interventions

Surgery
salpingectomy by open surgery
salpingo(s)tomy by open surgery
salpingectomy by laparoscopy
salpingo(s)tomy by laparoscopy

Medical treatment
methotrexate
hyperosmolar glucose
prostaglandins
potassium chloride
sodium chloride
actinomycin D
etoposide
mifepristone
danazol
anti hCG antibodies

Expectant management
no therapeutic intervention, only serum hCG monitoring

Types of outcome measures

As a result of the heterogeneity of treatments, the definition used for treatment success and failure in and between studies is not uniform. Therefore, in this review the following outcome measures are defined and analyzed:

Primary outcome
primary treatment success, defined as an uneventful decline of serum hCG to undetectable levels by the initial treatment. Therefore, treatment failures were regarded as re-interventions (surgical or medical) for clinical symptoms or inadequately declining serum hCG levels, i.e. persistent trophoblast.

Secondary outcomes
persistent trophoblast, defined as rising or plateauing serum hCG concentrations postoperatively or after medical treatment or expectant management for which additional treatment (surgical or medical) was needed

- tubal preservation
- complications/side effects
- patients' health related quality of life
- financial costs
- tubal patency, defined as the passage of dye at hysterosalpingogram or at second look laparoscopy through the homolateral tube and, if applicable, with inclusion of those patients in the denominator who were not eligible for hysterosalpingogram or second look laparoscopy because they had undergone a salpingectomy
- future fertility, defined as the occurrence of subsequent spontaneous pregnancy and pregnancy outcome (intrauterine pregnancy, repeat ectopic pregnancy) in patients with desiring future pregnancy

Search methods for identification of studies

This review was drawn on the search strategy developed for the Menstrual Disorders and Subfertility Group. We identified relevant trials from the Cochrane Menstrual Disorders and Subfertility Group's specialized register of controlled trials (searched up to February 2006). The following strategies were also adopted using the OVID platform see Appendix 1

In addition, monthly literature searches were done by the clinical librarians of the Department of Obstetrics and Gynaecology, Academic Medical Center, University of Amsterdam, in MEDLINE with the search strategy "ectopic pregnancy" and/or "tubal ectopic pregnancy" (searched January 1995 to July 2006). Moreover, an effort was made to identify and to include unpublished trials for instance by searching the Current Controlled Trials Register on the Internet (www.controlledtrials.com, July 2006) and searching the abstract books of the annual ESHRE and ASRM conventions.

Data collection and analysis

Two review authors inspected all citations identified by the search strategies. We obtained abstracts of all citations to identify eligible studies and obtained full reports of all eligible studies. PH and BM independently assessed whether the studies met the inclusion criteria for this review. Since 2004, this was done by PH and FM. Studies that were excluded are presented in the 'Characteristics of excluded studies' table with reasons for exclusion. Since 2004, PH and BM independently extracted data and assessed the quality of all studies eligible for this review. Differences of opinion were registered and resolved by consensus with all review authors.

The included trials were analyzed for the following quality criteria and methodological details. This information, if available, is presented in the table of included studies. If possible, missing data was sought from the authors. Differences of opinion were registered and resolved by consensus with all review authors.

Trial characteristics
1. method of randomization
2. quality of allocation concealment
3. extent of blinding
4. power calculation performed beforehand
5. funding
6. medical ethical committee approval

7. single or multicenter trial
8. intention-to-treat analysis
9. number of women randomised, details on dropouts or lost to follow up
10. duration, timing and location of the study

Types of participants
1. diagnosis of ectopic pregnancy (by a transvaginal sonographic finding of an ectopic gestational sac with an empty uterus, by a serum hCG discriminatory zone principle with an empty uterus, or by laparoscopy or laparotomy or all of the aforementioned)
2. (upper limit) serum hCG concentration
3. tubal pregnancy size
4. presence of fetal cardiac activity
5. presence of hemoperitoneum

Interventions
1. type of surgery
2. used drug for medical treatment
3. dosage and route of administration of medical treatment
4. expectant management

Primary outcome
treatment success by initial treatment

Secondary outcomes
1. persistent trophoblast
2. tubal preservation
3. complications/side effects
4. patients' health related quality of life
5. costs
6. tubal patency
7. future fertility (subsequent intra uterine pregnancy and repeat ectopic pregnancy)

Statistical analysis was performed according to the statistical guidelines for reviewers in the Cochrane Menstrual Disorders and Subfertility Group. Two by two tables were generated for each study for the dichotomous outcome measures. The effects in each study were expressed as odds ratios (OR) with 95% confidence intervals. If there were sufficient data, a summary statistic for each outcome was calculated using the Peto method (fixed-effect model).
Heterogeneity between the results of different studies was examined by inspecting the scatter in the data points on the graphs and the overlap in their confidence intervals, and by checking the I-square (I2) statistic. A value of greater than 50% was considered substantial heterogeneity. In case of statistical heterogeneity the original trials were studied for clinical heterogeneity.

Attempts were made to obtain missing data in the original article to perform analyses for the outcomes defined by contacting the principal authors.

RESULTS

Description of studies

Sixty nine reports were found eligible from the citations identified by the search strategy.

Eight studies were excluded because treatments were non randomly allocated see Characteristics of excluded studies: Lund 1955; Koninckx 1991; Murphy 1992; Laatikainen 1993; O'Shea 1994; Porpora 1996; Colacurci 1998; Kaya 2002).

Four studies were published in Chinese. These studies are awaiting assessment by the review authors because they still have to be translated. (Peng 1997; Su 2002; Hu 2003; Wei 2003) see Characteristics of studies awaiting classification

Five studies are ongoing (Hajenius 1 and Hajenius 2, Amsterdam, The Netherlands; Jurkovic, London, United Kingdom; Fernandez 1 and Fernandez 2, France, Current Controlled Trials Register) see Characteristics of ongoing studies.

Seven studies had published their results in more than one report (double publication).

- primary study Lundorff 1991a and double publication of Lundorff 1993a; Lundorff 1993b; Lindblom 1997; Lundorff 1997
- primary study Fernandez 1990 and double publication Fernandez 1991
- primary study Fernandez 1995 and double publication of Fernandez 1996
- primary study Rozenberg 2003 and double publication of Garbin 2004

Six studies reported their follow up data or other secondary outcomes or both in another report

- primary study Lundorff 1991a and follow-up data in Lundorff 1991b; Lundorff 1992; Gray 1995
- primary study Vermesh 1989 and follow-up data in Vermesh 1992
- primary study Hajenius 1997 and follow-up data in Nieuwkerk 1998a, Mol 1999a, Dias Pereira 1999
- primary study Sowter 2001a and follow-up data in Sowter 2001b
- primary study Gjelland 1995 and follow-up data in Hordnes 1997
- primary study Yalcinkaya 1996 and follow-up data in Yalcinkaya 2000

Thus in this review, 35 studies have been analysed on the treatment of tubal ectopic pregnancy, describing 25 different comparisons grouped into see Characteristics of included studies:

1. surgery

2. medical treatment

- methotrexate versus surgery
- methotrexate different administration route
- methotrexate different dosage/suspension
- methotrexate versus/or in combination with other medical treatment(s)
- hyperosmolar glucose

3. expectant management
One study was translated from Chinese to English (Wang 1998). One study had two different comparisons that have been analysed separately (Fernandez 1998).

Six authors were contacted for missing data in the original article to perform analyses for the outcomes defined (Dr Fujishita, Japan,

Dr Fernandez, France, Dr Rozenberg, France, Dr Hines, USA , Dr Yalcinkaya, USA and Dr. El Sherbiny, Egypt) and they responded.

The studies were carried out in 19 different countries: Austria (Lang 1990; Egarter 1991), Canada (Tulandi 1991a), China (Wang 1998), Egypt (Elmoghazy 2000; El-Sherbiny 2003), Finland (Korhonen 1996), France (Fernandez 1991; Fernandez 1994; Fernandez 1995; Fernandez 1998; Rozenberg 2003), Greece (Tzafettas 1994), India (Sharma 2003), Iran (Alleyassin 2006), Israel (Shulman 1992; Sadan 2001), Italy (Fedele 1998), Japan (Fujishita 1995b; Fujishita 2004), Netherlands (Hajenius 1997; Dias Pereira 1999; Nieuwkerk 1998a; Mol 1999a), New Zealand (Sowter 2001a; Sowter 2001b), Norway (Gjelland 1995; Hordnes 1997), Sweden (Lundorff 1991a; Lundorff 1991b; Lundorff 1992; Gray 1995; Landstrom 1998), Turkey (Ugur 1996), United Kingdom (Gazvani 1998), United Stated of America (Vermesh 1989; Vermesh 1992; Mottla 1992; Cohen 1996; Graczykowski 1997; Saraj 1998; Yalcinkaya 1996; Yalcinkaya 2000; Klauser 2005).

Further details about the included studies are provided in the table Table 1

Surgery

1. Laparoscopic salpingostomy versus salpingostomy by open surgery (Vermesh 1989; Lundorff 1991a; Lundorff 1991b; Lundorff 1992; Vermesh 1992; Gray 1995)

2. Minilaparotomy versus laparotomy (Sharma 2003)

3. Salpingostomy without tubal suturing versus salpingostomy with tubal suturing (Tulandi 1991a; Fujishita 2004)

4. Salpingostomy alone versus salpingostomy combined with medical treatment
a. with a single dose intramuscular methotrexate (Graczykowski 1997; Elmoghazy 2000)
b. with an intra mesosalpingeal injection vasopressin (Ugur 1996)
c. with an intra mesosalpingeal injection oxytocin (Fedele 1998)

Medical Treatment

Methotrexate versus surgery

5. Systemic methotrexate versus laparoscopic salpingostomy
a. in a fixed multiple dose intramuscular regimen (Hajenius 1997; Nieuwkerk 1998a; Dias Pereira 1999; Mol 1999a)
b. in a variable dose intramuscular regimen (Fernandez 1998; Saraj 1998; Sowter 2001a; Sowter 2001b; El-Sherbiny 2003)

6. Local methotrexate versus laparoscopic salpingostomy
a. transvaginally under sonographic guidance (Fernandez 1995; Fernandez 1998)
b. under laparoscopic guidance (Mottla 1992; Zilber 1996)

Methotrexate via different administration routes

7. transvaginally under sonographic guidance versus under laparoscopic guidance (Tzafettas 1994)
8. transvaginally under sonographic guidance versus single dose intramuscular (Fernandez 1994; Fernandez 1998; Cohen 1996)
9. under laparoscopic guidance versus the same regimen in combination with systemic intramuscular methotrexate (Shulman 1992)

Methotrexate different dosage/suspension

10. Single dose versus fixed multiple dose both by intramuscular administration (Klauser 2005; Alleyassin 2006)
11. 25 mg/m2 methotrexate versus the standard 50 mg/m2 methotrexate both in a single dose intramuscular regimen (Yalcinkaya 1996; Yalcinkaya 2000)
12. in lipiodol suspensions versus in saline both under laparoscopic guidance (Fujishita 1995b)

Methotrexate versus/or in combination with other medical treatments

13. Methotrexate versus prostaglandins both transvaginally under sonographic guidance combined with the systemic administration of the drug (Fernandez 1991)
14. Systemic methotrexate in a single dose intramuscular regimen alone versus in combination with oral mifepristone (Gazvani 1998; Rozenberg 2003)
15. Systemic methotrexate in a single dose intramuscular regimen alone versus in combination with Ectopic Pregnancy 2 (EP2) decoction (Chinese herb) (Wang 1998)

Hyperosmolar glucose

16. Hyperosmolar glucose intratubal under laparoscopic guidance versus other treatments
a. versus local methotrexate under laparoscopic guidance (Sadan 2001)
b. versus hyperosmolar glucose transvaginally under sonographic guidance (Gjelland 1995; Hordnes 1997)
c. versus local and systemic prostaglandins (Lang 1990)
d. together with local prostaglandins versus methotrexate in a oral regimen (Landstrom 1998)

Expectant management

17. expectant management versus medical treatment
a. versus systemic methotrexate in a low dose oral regimen (Korhonen 1996)
b. versus local and systemic prostaglandins (Egarter 1991)

Risk of bias in included studies

The overall methodological risk of bias of the included 35 studies was considered sub-optimal, largely due to the lack of detailed information on allocation and randomization in more than half of the studies. Further details of trials quality can be found in the table seeTable 1

Method of randomization

All 35 studies stated that randomised allocation had occurred. Nineteen trials described the method of allocation (Vermesh 1989; Lang 1990; Fernandez 1991; Mottla 1992; Fernandez 1994; Fernandez 1995; Cohen 1996; Korhonen 1996; Graczykowski 1997; Hajenius 1997; Fedele 1998; Fernandez 1998; Gazvani 1998; Sowter 2001a; El-Sherbiny 2003; Rozenberg 2003; Sharma 2003; Fujishita 2004; Alleyassin 2006).

Allocation concealment

Eleven studies described concealed allocation (Vermesh 1989; Fernandez 1994; Cohen 1996; Korhonen 1996; Hajenius 1997; Fedele 1998; Gazvani 1998; Yalcinkaya 2000; Sowter 2001a; Rozenberg 2003; Alleyassin 2006).

Blinding

For most comparisons blinding of treatment was not applicable. Two studies employed double blinding (Yalcinkaya 1996; update Yalcinkaya 2000; Sadan 2001), whereas two studies were placebo controlled double blinded (Korhonen 1996; Rozenberg 2003). The code was opened after the end of treatment of the last patient.

Power calculation
Nine studies reported a power calculation beforehand (Egarter 1991; Korhonen 1996; Hajenius 1997; Gazvani 1998; Yalcinkaya 2000; Sowter 2001a; Rozenberg 2003; Fujishita 2004; Alleyassin 2006).

Sample size
All studies had small sample sizes. Only six studies included 100 women or more (Hajenius 1997 n = 100; Graczykowski 1997 n = 129, Fernandez 1998 n = 100; Yalcinkaya 2000 n = 100; Rozenberg 2003 n = 212; Alleyassin 2006 n = 108).
Meta-analysis was possible for eight comparisons involving 60 to 265 women (comparisons 1, 3, 4, 5b, 6b, 8, 10 and 14).

Dropouts
The number of exclusions after randomization was mentioned in four studies (Lundorff 1991a; Mottla 1992; Hajenius 1997; Saraj 1998).
One (1%) patient was excluded after randomization in the study of Saraj 1998 (no ectopic pregnancy) and four (29%) in the study of Lundorff 1991a (non tubal pregnancy and technical difficulties). The high rate in the study of Mottla 1992 of 43% (9/21) and in the study of Hajenius 1997 of 29% (40/140) was the result of secondary exclusions at laparoscopy (i.e. tubal rupture, active bleeding, no tubal ectopic pregnancy, size of the ectopic pregnancy, non visibility of the pelvis), as women were randomised before a confirmative laparoscopy. Hajenius 1997 wrote that randomization at laparoscopy could have overcome these secondary exclusions, but the ethics committees judged a design in which women did not know the randomization outcome before surgery to be unethical. To prevent potential selection bias, the secondary exclusion criteria were assessed by a surgeon unaware of the randomization outcome. In a follow up study of this trial reporting on the health related quality of life, eleven of the 100 women (11%) had insufficient Dutch or English language skills to complete the questionnaires (Nieuwkerk 1998a).

Premature stopping of the trial
Four studies were stopped prematurely. The study of Mottla 1992 comparing methotrexate under laparoscopic guidance versus laparoscopic salpingostomy was stopped prematurely because of disappointing results in the medically treated group, without mentioning of a preplanned stopping rule. The study of Sadan 2001 comparing methotrexate versus hyperosmolar glucose both under laparoscopic guidance was discontinued after an interim analysis of the data of 20 patients due to a higher failure rate in the hyperosmolar glucose group. The study of Egarter 1991 comparing prostaglandins with expectant management was stopped prematurely after the first intermediate analysis because primary treatment success was less in the expectant group. The study of Rozenberg 2003 was stopped after the second interim analysis because criteria of the stopping rule were met. This stopping rule was based on the triangular test described by Whitehead 1992.

Publication
All studies but four were published as a full paper. Those four were published as a conference abstract only (Yalcinkaya 1996; Elmoghazy 2000; Yalcinkaya 2000; Klauser 2005).

Lost to follow up
The loss to follow up for future fertility was mentioned in ten studies and varied between 0.9% (Rozenberg 2003), 1% (Lundorff 1992), 2.4% (Yalcinkaya 1996), 10% (Dias Pereira 1999), 11% (Graczykowski 1997), 14% (Sowter 2001a) and 18% (Fernandez 1998), 25% (Vermesh 1992), 44% (Yalcinkaya 2000) and 47% (Tulandi 1991a).
In a follow-up study of the trial of Hajenius 1997 reporting on health related quality of life, 5.6% did not return any of the questionnaires (Nieuwkerk 1998a).

Effects of interventions

Surgery
1. Laparoscopic salpingostomy versus salpingostomy by open surgery
The combined results of two studies, involving 165 hemodynamically stable women with a small unruptured tubal ectopic pregnancy (Vermesh 1989; Lundorff 1991a), show laparoscopic salpingostomy to be significantly less successful than the open surgical approach in the elimination of the tubal ectopic pregnancy (OR 0.28, 95% CI 0.09 to 0.86). This mainly resulted from the significant higher persistent trophoblast rate of laparoscopic surgery (OR 3.5, 95% CI 1.1 to 11).

Laparoscopic surgery was significantly less costly than open surgery (Gray 1995). Mean costs were 28,058 versus 32,699 Swedish kronor, P = 0.03 (€ 3127 versus 3644). These cost savings were the result of significantly shorter operation time (73 versus 88 minutes, P < 0.001), less perioperative blood loss (79 versus 195 ml, P < 0.01), shorter duration of hospital stay (1 and 2 versus 3 and 5 days, P < 0.01), and shorter convalescence time (11 versus 24 days, P < 0.001).

There was a non significant tendency to a lower tubal patency rate after laparoscopic surgery (OR 0.58, 95% CI 0.23 to 1.4), which was assessed in 110 women after a follow up of one to 29 weeks (Vermesh 1989; Lundorff 1991b).

Long term follow up was assessed in 127 women who desired future fertility (Lundorff 1992; Vermesh 1992). The number of subsequent intrauterine pregnancies showed no evidence of a difference (OR 1.2, 95% CI 0.59 to 2.5) and there was a non significant tendency to a lower repeat ectopic pregnancy rate (OR 0.47, 95% 0.15 to 1.5).

2. Minilaparotomy versus laparotomy
In a study, involving 60 women with an ectopic pregnancy (Sharma 2003), all women were successfully treated. In women randomized for minilaparotomy without using packs or retractors no conversions to a conventional laparotomy were necessary. In the conventional laparotomy group the incision was vertical in 22 of the 30 patients.

Postoperative complications were significantly less in the minilaparotomy group than in the conventional laparotomy group (paralytic ileus 10% versus 27%, P = 0.045, wound infection 3% versus 17%, P = 0.045).

Parameters of costs were significantly less in the minilaparotomy group than in the conventional laparotomy group (mean operative time: 38 versus 54 min, P = 0.033 and discharge 3.4 versus 6.9 days, P = 0.015).

No data are available on tubal patency or future fertility.

3. Salpingostomy without tubal suturing versus salpingostomy with tubal suturing
The combined results of two studies, involving 109 women with an unruptured ampullary ectopic pregnancy (Tulandi 1991a; Fujishita

2004), show that there was a non significant tendency to a lower treatment success after salpingostomy without tubal suturing than when the tube was sutured (OR 0.16, 95% CI 0.02 to 1.23). This was the result of four women with persistent trophoblast in the group in which the tube was left open for secondary healing. These women were additionally successfully treated with methotrexate.

There was a non significant tendency to a lower tubal patency rate after salpingostomy without tubul suturing (OR 0.38, 95% CI 0.06 to 2.4).

Future fertility was assessed in 88 women. No evidence of a difference was found in the number of subsequent intrauterine pregnancies (OR 1.1, 95% CI 0.44 to 2.6) and the number of repeat ectopic pregnancies (OR 1.2, 95% CI 0.38 to 3.8).

4. Salpingostomy alone versus combined with medical treatment

a. with a single dose intramuscular methotrexate

The results of two studies, involving 163 women with a tubal ectopic pregnancy (Graczykowski 1997; Elmoghazy 2000), show that salpingostomy alone was significantly less successful (OR 0.25, 95% CI 0.08 to 0.76), due to the higher incidence of persistent trophoblast (OR 4.1, 95% CI 1.3 to 13) than when a prophylactic single dose of systemic methotrexate (1 mg/kg IM) was given within 24 hours postoperatively.

Side effects of the prophylactic methotrexate therapy, occurring in 5.5 to 8% of women, were mild.

No data are available on tubal patency or future fertility.

b. with an intra mesosalpingeal injection vasopressin

A study, involving 40 hemodynamically stable women with a small unruptured ectopic pregnancy (Ugur 1996), shows that when a salpingostomy was done without an intra mesosalpingeal vasopressin injection there was a non significant tendency to a lower treatment success, due to more conversions to open surgery for uncontrollable bleeding than when vasopressin was prophylactic injected intra mesosalpingeal (OR 0.35, 95% CI 0.09 to 1.5).

Tubal patency was assessed in 31 women who underwent hysterosalpingography. There was a non significant tendency to a lower tubal patency rate after salpingostomy without an intra mesosalpingeal vasopressin injection (OR 0.42, 95% CI 0.10 to 1.9).

No data are available on future fertility.

c. with an intra mesosalpingeal injection oxytocin

A multicenter study, involving 25 hemodynamically stable women with a small unruptured ectopic pregnancy (Fedele 1998), reports that an intra mesosalpingeal injection of 20 IU oxytocin diluted in 20 ml saline three minutes before tubal incision significantly reduced intra- and postoperative blood loss with an easier removal of the tubal ectopic pregnancy (P < 0.05) without side effects. These positive effects of intra mesosalpingeal injection of oxytocin, however, were not reflected in primary treatment success (OR 0.15, 95% CI 0.00 to 7.3).

No data are available on tubal patency or future fertility.

Medical treatment

Methotrexate versus surgery

5. Systemic methotrexate versus laparoscopic salpingostomy

a. in a fixed multiple dose intramuscular regimen

In a multicenter study, 100 hemodynamically stable women with a laparoscopically confirmed unruptured tubal ectopic pregnancy without fetal cardiac activity and no signs of active bleeding were randomized between systemic methotrexate (1 mg/kg bodyweight intramuscularly day 0, 2, 4, 6 alternated with folinic acid 0.1 mg/kg bodyweight orally day 1, 3, 5, 7) and laparoscopic salpingostomy (Hajenius 1997). There were no limits on serum hCG concentration or size of the tubal ectopic pregnancy. The mean serum hCG concentration in women treated with methotrexate was 1950 IU/l (110 to 19,500). There was a non significant tendency to a higher treatment success with systemic methotrexate treatment (OR 1.8, 95% CI 0.73 to 4.6).

No significant differences were found in tubal preservation (OR 0.82, 95% CI 0.21 to 3.2).

Sixty one per cent of the patients undergoing systemic methotrexate therapy experienced complications or side effects compared to only 12% in the salpingostomy group. In the salpingostomy group virtually all complications comprised the side effects of systemic methotrexate in women treated for persistent trophoblast.

Health related quality of life was more severely impaired after systemic methotrexate than after laparoscopic salpingostomy (Nieuwkerk 1998a). Medically treated women showed more limitations in physical functioning, role functioning, and social functioning, had worse health perceptions, less energy, more pain, more physical symptoms, a worse overall quality of life, and were more depressed than surgically treated women (P < 0.05).

Systemic methotrexate treatment was significantly more expensive than laparoscopic salpingostomy (Mol 1999a). Mean total costs per patient were $5721 for systemic methotrexate and $4066 for laparoscopic salpingostomy with a mean difference of $1655 (95% CI 906 to 2414). The costs of the confirmative laparoscopy in the methotrexate group were included, whereas in every day practice this would not occur in women with ectopic pregnancy having methotrexate. However, re-interventions, only required in women with initial serum hCG concentrations > 1500 IU/l, generated considerable additional costs in the methotrexate group due to prolonged hospital stay (4.5 versus 2.5 days). Furthermore, costs due to productivity loss were higher in the systemic methotrexate group (lost labor days 38 versus 28).

Subgroup analysis indicated that only in women with an initial serum hCG concentration < 1500 IU/l the difference in total costs between systemic methotrexate ($4399) and laparoscopic salpingostomy ($4185) was less, however not significantly ($214, 95% CI -283 to 676). In a scenario analysis, it was calculated that systemic methotrexate was less costly compared to laparoscopic salpingostomy, only if administered as part of a totally noninvasive treatment strategy and in women with an initial serum hCG concentration < 1500 IU/l (total costs $2991). In such a scenario without a confirmative laparoscopy, total costs were equal to laparoscopic salpingostomy in women with an initial serum hCG concentration varying between 1500 - 3000 IU/l ($3885), whereas in women with an initial serum hCG concentration > 3000 IU/l systemic methotrexate would still be more costly ($4975) (Mol 1999a).

Tubal patency rate, assessed in 81 women, did not differ (OR 0.84, 95% CI 0.35 to 2.0).

Fertility outcome was assessed in 74 women trying to conceive 18 months after completion of the treatment. No significant differences were found for spontaneous intrauterine pregnancy (OR 0.82, 95% CI 0.32 to 2.1) and repeat ectopic pregnancies (OR 0.87, 95% CI 0.19 to 4.1) (Dias Pereira 1999).

b. in a variable dose intramuscular regimen

The combined results of four studies, involving 265 hemodynamically stable women with a small unruptured tubal ectopic pregnancy (Fernandez 1998; Saraj 1998; Sowter 2001a; Sowter 2001b, El-Sherbiny 2003) show that one single dose of systemic methotrexate intramuscularly (50 mg/m2 or 1 mg/kg bodyweight) was significantly less successful than laparoscopic salpingostomy in the elimination of tubal ectopic pregnancy (OR 0.38, 95% CI 0.20 to 0.71). This was mainly the result from inadequately declining serum hCG concentrations for which additional methotrexate injections were given (OR 3.3, 95% CI 1.7 to 6.7). Pooling the data, there was substantial heterogeneity (I2 of 52%).

Twenty seven of the 120 women treated with a one single dose of methotrexate had inadequately declining serum hCG concentrations. Of these 27 women, four were treated surgically, whereas 23 were given additional methotrexate injections, all but three successfully. Of the 20 women successfully treated with additional methotrexate, 17 women received a total of two doses, two women a total of three doses, and one woman a total of four doses. With a variable dose methotrexate regimen treatment success rises, but shows no evidence of a difference with laparoscopic salpingostomy (OR 1.1, 95% CI 0.52 to 2.3).

No adverse events were reported in the laparoscopy group while four women in the methotrexate group had side effects (two had minor mouth ulceration, two women had dry eyes and one woman experienced a dry vagina) (Sowter 2001a).

Selection criteria used in the studies were an upper limit of serum hCG (< 5000 IU/l, Sowter 2001a, < 10,000 IU/l El-Sherbiny 2003), absence of positive fetal heartbeat (Saraj 1998; Sowter 2001a, El-Sherbiny 2003), small size of the tubal ectopic pregnancy (< 3.5 cm Saraj 1998; Sowter 2001a, < 4 cm, El-Sherbiny 2003) and a pretherapeutic score < 13 (Fernandez 1998). Mean serum hCG concentrations in women treated with methotrexate were 3120 IU/l (Fernandez 1998) 3162 IU/l (Saraj 1998), 927 IU/l (Sowter 2001a) and 2274 IU/l (El-Sherbiny 2003).

Women treated with methotrexate had a significantly better physical functioning than after laparoscopic surgery (significant differences in SF36 physical functioning was seen in favor of methotrexate on day 4 of follow up but not in the other dimensions of the SF 36 or in anxiety and depression scores, P < 0.01). No differences were found in psychological functioning (Sowter 2001a).

Single dose methotrexate resulted in a 52% saving in direct costs compared to laparoscopic surgery: mean direct costs per patient were $ NZ 1470 (€ 787) and $ NZ 3083 (€ 1650), respectively. This significant difference of $ NZ 1613 (95% CI 1166 to 2061) (€ 863, 95% CI 624 to 1103) resulted from savings due to reduced theatre usage and hospital stay. Furthermore, single dose methotrexate resulted in a 40% saving in indirect costs: mean indirect costs per patient were $ NZ 1141 (€ 610) and $ NZ 1899 (€ 1016), respectively, with a mean difference of $ NZ 758 (95% 277 to 1240) (€ 406, 95% CI 148 to 664).

Subgroup analysis indicated that in women with an initial serum hCG concentration > 1500 IU/l the difference in indirect costs was lost due to the prolonged follow up and a higher rate of surgical re-interventions (Sowter 2001b). In a scenario analysis, it was calculated that the cost savings of single dose methotrexate remained under a wide range of alternative assumptions about unit costs.

In 115 women tubal patency could be assessed (Saraj 1998; Sowter 2001a, El-Sherbiny 2003) and did not show significant differences between the two treatment groups (OR 1.5, 95% CI 0.69 to 3.1).

Future fertility was assessed in 98 women. No significant differences were found in the number of subsequent intra uterine pregnancies (OR 1.0, 95% CI 0.43 to 2.4), whereas there was a non significant tendency to a lower repeat ectopic pregnancy rate (OR 0.54, 95% CI 0.12 to 2.4) (Fernandez 1998; Saraj 1998, El-Sherbiny 2003).

6. Local methotrexate versus laparoscopic salpingostomy

a. transvaginally under sonographic guidance

A study, that was updated in 1998, involving 78 women with an ectopic pregnancy with a pre-therapeutic score < 13 (Fernandez 1998), shows that methotrexate 1 mg/kg bodyweight transvaginally under sonographic guidance was significantly less successful than laparoscopic salpingostomy in the elimination of the tubal ectopic pregnancy (OR 0.17, 95% CI 0.04, to 0.76). This was mainly the result from the higher persistent trophoblast rate (OR 4.9, 95% CI 0.99 to 24) for which additional systemic methotrexate injections were necessary. In all patients additional interventions were successful, which is reflected in a 100% tubal preservation rate. Mean serum hCG concentrations in women treated with local methotrexate was 3805 IU/l.

In the original report where 40 women were randomized (Fernandez 1995), homolateral tubal patency was assessed in 35 women and no difference was found (OR 0.94, 95% CI 0.12 to 7.3).

Future fertility was assessed in 51 women. The number of subsequent intrauterine pregnancies was significantly higher (OR 4.1, 95% CI 1.3 to 14) after local methotrexate treatment, and there was a non significant tendency to a lower repeat ectopic pregnancy rate (OR 0.30, 95% CI 0.05 to 1.7).

b. under laparoscopic guidance

The combined results of two studies, involving 60 hemodynamically stable women with a small unruptured tubal ectopic pregnancy without signs of active bleeding (Mottla 1992; Zilber 1996), show a non significant tendency to a lower treatment success of 25 mg methotrexate under laparoscopic guidance compared to laparoscopic salpingostomy (OR 0.26, 95% CI 0.06 to 1.1). Mean serum hCG concentrations in women treated with local methotrexate were 1214 IU/l (Zilber 1996). In the study by Mottla 1992, the initial rise in serum hCG after installing local medical treatment was wrongly interpreted as treatment failure by the authors, because they were apparently unfamiliar with the serum hCG clearance patterns after methotrexate. These women were surgically treated for persistent trophoblast (OR 3.9, 95% CI 0.93 to 16). These additional surgical interventions had no significant impact on tubal preservation (OR 0.16, 95% CI 0.01 to 2.5).

One study (Zilber 1996) reports on future fertility in 34 women. No significant difference was found for subsequent intrauterine pregnancies (OR 0. 87, 95% CI 0.15 to 5.0), whereas there was a non significant tendency to a lower repeat ectopic pregnancy rate (OR 0.15, 95% CI 0.00 to 7.7).

Methotrexate via different administration routes

7. Transvaginally under sonographic guidance versus under laparoscopic guidance

The results of a study, involving 36 hemodynamically stable women with a small unruptured ectopic pregnancy (Tzafettas 1994), show that treatment success of 100 mg methotrexate administered transvaginally under ultrasound guidance was significantly better than the 'blind' intra-tubal injection of 100 mg methotrexate under laparoscopic guidance (OR 5.8, 95% CI 1.3 to 26).

No data are available on tubal patency and future fertility.

8. Transvaginally under sonographic guidance versus single dose intramuscular

The combined results of three studies, involving 95 women with a small unruptured ectopic pregnancy (Fernandez 1994; Cohen 1996; Fernandez 1998), show a non significant tendency to a higher primary treatment success after local methotrexate (OR 2.14, 95% CI 0.82 to 5.6). In the local methotrexate group the tubal content was aspirated and methotrexate 1 mg/kg was administered. Only one woman developed mild side effects and she was treated by single dose methotrexate (50 mg/m2).

Fertility outcome was assessed in 51 women. No significant differences were found in the number of subsequent intrauterine pregnancies (OR 1.5, 95% CI 0.43 to 5.3) and repeat ectopic pregnancies (OR 4.1, 95% CI 0.05 to 307). Pooling the data for intra uterine pregnancies, there was a substantial heterogeneity (I2 of 72%).

9. Under laparoscopic guidance versus the same regimen in combination with systemic methotrexate intramuscular

In a study, involving only 15 hemodynamically stable women with a small unruptured tubal ectopic pregnancy (Shulman 1992), there was a non significant tendency to a lower primary treatment success after local methotrexate alone (12.5 mg) than when this regimen was combined with systemic methotrexate (0.5 mg/kg orally for five days alternated with folinic acid) (OR 0.12, 95% CI 0.0 to 6.0).

No complications or side effects were seen in both treatment groups.

No data are available on tubal patency and future fertility.

Methotrexate different dosage/suspension

10. Single dose versus fixed multiple dose both by intramuscular administration

The results of two studies, involving 159 women with a clinical diagnosis of ectopic pregnancy (Klauser 2005; Alleyassin 2006), show no significant difference in primary treatment success between the two treatment groups (OR 0.89, 95% CI 0.32 to 2.5). Mean serum hCG concentrations varied between 2230 to 2973 IU/l in the single dose group (50 mg/m2) and 2180 to 2244 IU/l in the multiple dose group (1 mg/kg). In the study of Alleyassin 2006 the six out of 54 women with an inadequate decline of the serum hCG concentration after single dose methotrexate were all successfully treated with a second dose.

Contradictory, the study of Klauser 2005 reported minor side effects of 28% in the single dose group versus 10% in the multiple dose group (P = 0.2). In the study of Alleyassin 2006 complications were reported of 28% in the single dose group versus 37% in the multiple dose group (P = 0.3).

No data are available on tubal patency and future fertility.

11. 25 mg/m2 versus the standard 50 mg/m2 both in a single dose intramuscular regimen

A double blinded study that was updated in 2000, (Yalcinkaya 1996; Yalcinkaya 2000), involving 100 hemodynamically stable women with an unruptured tubal ectopic pregnancy shows a non significant tendency to a lower treatment success after a lower dose of methotrexate compared to the standard 50 mg/m2 administration (OR 0.68, 95% CI 0.30 to 1.5). A second methotrexate injection for inadequately declining serum hCG concentrations was necessary in 31% (15/48) in the lower dose group and in 25% (13/52) in the standard group. Treatment success of this variable dose regimen did not differ between the two groups (OR 0.77, 95% CI 0.24 to 2.5). Mean serum hCG concentrations were 2405 IU/l (+/- 3204) and 2841 (+/- 4132) IU/l, respectively and fetal heart activity was present in two (4.2%) and seven (13.4%) women, respectively.

Side effects did not differ between the two groups.

Tubal patency, assessed in 37 women, did not differ between the two treatment groups (OR 0.90, 95% CI 0.25 to 3.2).

Future fertility was assessed in 56 women. No significant difference was found in the number of subsequent intrauterine pregnancies (OR 1.1, 95% CI 0.37 to 3.2). There was a non significant tendency to a lower repeat ectopic pregnancy rate in the lower dose group (OR 0.56, 95% CI 0.10 to 3.0).

12. Methotrexate in lipiodol suspensions versus methotrexate in saline both under laparoscopic guidance

From results of in vitro studies and animal experiments it was found that methotrexate dissolved in lipiodol suspensions with phosphatidylcholine added as a dispersing stabilizer, resulted in high tissue concentrations with prolongation of the drug effect (Fujishita 1995a). The results of a small study, involving 26 women with a small unruptured ectopic pregnancy without fetal cardiac activity (Fujishita 1995b), show that 20 to 50 mg methotrexate dissolved in lipidiol was significantly more successful than 20 to 50 mg methotrexate in saline in the elimination of the tubal ectopic pregnancy (OR 6.0, 95% CI 1.3 to 27) because persistent trophoblast rate was less in the lipidiol group (OR 0.22, 95% CI 0.05 to 1.1).

There was a non significant tendency to a higher tubal patency rate (OR 2.1, 95% CI 0.29 to 15) and a lower subsequent intrauterine pregnancy rate in the lipidiol group (OR 0.43, 95% CI 0.07 to 2.6).

Methotrexate versus/or in combination with other medical treatment

13. Methotrexate versus prostaglandins both transvaginally under sonographic guidance combined with the systemic administration of the drug

In a study, involving 21 hemodynamically stable women with a tubal ectopic pregnancy (Fernandez 1991), no significant difference was found in primary treatment success between methotrexate (1

mg/kg local and systemic) and prostaglandin therapy (OR 1.0, 95% CI 0.17 to 6.0). The authors do not mention the number of additional surgical interventions done per group.

Only one woman in each treatment group developed side effects.

There was a non significant tendency to a lower tubal patency rate in the methotrexate group (OR 0.17, 95% CI 0.0 to 9.1).

No data are available on future fertility.

14. Systemic methotrexate in a single dose intramuscular regimen alone versus in combination with oral mifepristone

The combined results of two studies, involving 262 hemodynamically stable women with an unruptured ectopic pregnancy without signs of active bleeding (Gazvani 1998; Rozenberg 2003), show that single dose methotrexate alone (50 mg/m2) was significantly less successful in the elimination of the tubal ectopic pregnancy than when 600 mg mifepristone (antiprogesterone) was added (OR 0.59, 95% CI 0.35 to 1.0). Persistent trophoblast occurred more frequent with methotrexate only (OR 1.4, 95% CI 0.69 to 2.7). In the study of Gazvani 1998, although all tubal pregnancies were laparoscopically confirmed, mean serum hCG concentrations were low in both treatment groups, i.e. 346 IU/l (range 52 to12,700) and 497 IU/l (range 30 to 4200), respectively. In the study of Rozenberg 2003, who used a diagnostic non-laparoscopic algorithm, mean serum hCG concentrations were 1679 IU/l (range 652 to 3658) and 1620 IU/l (range 805 to 3190), respectively.

In the study of Gazvani 1998 only two women in each treatment group developed side effects, whereas in the study of Rozenberg 2003 more side effects were seen (gastritis 30 versus 34, stomatitis 6 versus 8, reversible alopecia 3 versus 3 women).

No differences were found in tubal preservation (OR 0.73, 95% CI 0.37 to 1.4).

Tubal patency could only be assessed for 24 women. There was a non significant tendency to a lower tubal patency rate with methotrexate only (OR 0.38, 95% CI 0.05 to 3.1).

No data are available on future fertility.

15. Systemic methotrexate in a single dose intramuscular regimen alone versus in combination with Ectopic Pregnancy 2 (EP2) decoction

In a study, involving 78 women with a tubal ectopic pregnancy (Wang 1998) single dose methotrexate alone (50 to 70 mg/m2) was significantly less successful in the elimination of the tubal ectopic pregnancy than when Ectopic Pregnancy 2 (EP2) decoction -a Chinese herb- was added (OR 0.08, 95% CI 0.02 to 0.39).

The number of subsequent intrauterine pregnancies was significantly lower (OR 0.19, 95% CI 0.07 to 0.51), whereas there was a non significant tendency to a higher repeat ectopic pregnancy rate (OR 4.2, 95% CI 0.74 to 23).

Hyperosmolar glucose

16. Hyperosmolar glucose under laparoscopic guidance versus other treatments

a. versus methotrexate under laparoscopic guidance

In a double blinded study (Sadan 2001) there was a non significant tendency that hyperosmolar glucose was less successful than 25 mg methotrexate (OR 0.30, 95% CI 0.05 to 2.0) in the elimination of tubal ectopic pregnancy in hemodynamically stable women with a laparoscopically confirmed unruptured tubal ectopic pregnancy < 4 cm. This was the result of the higher intervention rate for persistent trophoblast in the hyperosmolar glucose group (OR 2.7, 95% 0.24 to 29) and surgical interventions for tubal rupture. The study was discontinued after interim analysis of the data of 20 women.

No data are available on tubal patency and future fertility.

b. versus hyperosmolar glucose transvaginally under sonographic guidance

The results of a study, involving 80 women with a small unruptured ectopic pregnancy and a serum hCG concentration < 3000 IU/l (Gjelland 1995), show that hyperosmolar glucose administered under laparoscopic guidance was significantly less successful than when administered transvaginally under sonographic guidance (OR 0.38, 95% CI 0.15 to 0.93). This was the result of both technical difficulties necessitating conversions to laparotomy even without installing the medical therapy, and surgical re-interventions for persistent trophoblast in the laparoscopy group (OR 2.0, 95% CI 0.74 to 5.2).

In a follow-up study the author does not mention tubal patency per treatment group (Hordnes 1997).

Future fertility was assessed in 36 women. There was a non significant tendency to a higher subsequent intrauterine pregnancy rate (OR 3.3, 95% CI 0.88 to 12) and repeat ectopic pregnancy rate (OR 1.7, 95% CI 0.29 to 10) in the group administered under laparoscopic guidance.

c. versus local and systemic prostaglandins

In a study, involving 31 women with a unruptured tubal ectopic pregnancy and an urinary hCG concentration < 5000 IU/l (Lang 1990), there was a non significant tendency to a higher primary treatment success after hyperosmolar glucose (OR 8.5, 95% CI 0.51 to 142).

Side effects were only seen in the prostaglandin group and occurred in 60% of the patients.

No difference was found in tubal patency rate (OR 0.73, 95% CI 0.04 to 13) between the two treatment groups, assessed in 14 women.

No data are available on future fertility.

d. together with local prostaglandins versus systemic methotrexate in a oral regimen

In a multicenter study, involving 31 hemodynamically stable women with a laparoscopically confirmed unruptured tubal ectopic pregnancy and a serum hCG concentration < 3000 IU/l (Landstrom 1998), there was a non significant tendency to a lower primary treatment success of the local injection therapy (OR 0.60, 95% CI 0.06 to 6.3) compared to a noninvasive oral management with methotrexate. Mean serum hCG concentrations, however, were low, i.e. 932 IU/l (range 54 to 4446) and 810 IU/l (range 104 to 3085), respectively.

No data are available on tubal patency or future fertility.

Expectant management

17. Expectant management versus medical treatment

a. versus systemic methotrexate in a low dose oral regimen

In a double blinded placebo controlled study, involving 60 hemodynamically stable women with a small tubal ectopic pregnancy without fetal cardiac activity and a serum hCG concentration < 5000 IU/l (Korhonen 1996), no significant differences were found in primary treatment success (OR 1.0, 95% CI 0.31 to 3.3) between expectant management and 2.5 mg/kg oral methotrexate for five days. However, mean serum hCG concentrations were low, i.e. 211 IU/l (range 20 to 1343) in the expectant group and 395 IU/l (range 61 to 4279) in the methotrexate group. In this placebo controlled trial 23% of the patients in both treatment groups needed surgical intervention. The authors did not mention which patients failed, why they failed and how they were managed subsequently.

No data are available on tubal patency or future fertility.

b. versus local and systemic prostaglandins
The results of a small placebo controlled study, involving 23 women with an unruptured ectopic pregnancy and a serum hCG concentration < 2500 IU/l (Egarter 1991), show that expectant management was significantly less successful than prostaglandin therapy (OR 0.08, 95% CI 0.02 to 0.39). No side effects were reported.

No data are available on tubal patency and future fertility.

DISCUSSION

In this review on the treatment of tubal ectopic pregnancy, 35 studies have been analyzed with 25 different comparisons. These comparisons have been grouped into three categories; (1) surgery, (2) medical treatment and (3) expectant management. Many comparisons only had a single small scale study. Small numbers, especially in the assessment of fertility outcome, made it difficult to obtain reliable comparisons of the various outcome measures.
The methodological quality of the 35 included studies was poor. In 53% the randomization procedure was specified, whereas in only 32% the allocation was concealed.
In about half of the studies the authors focused on short term outcome (the elimination of the tubal ectopic pregnancy). In the evaluation of therapies for tubal ectopic pregnancy short term effectiveness alone is not the proper outcome measure because the tubal ectopic pregnancy will be eventually eliminated in all women, either by primary treatment alone or in combination with additional interventions. Therefore, it is important to focus on treatment strategies as a whole, including side effects, treatment burden, costs and last but not least future fertility outcome.

Surgery

Laparoscopic salpingostomy is feasible in women with a tubal ectopic pregnancy with reduced costs compared to the open surgical approach. This benefit should be balanced against a significant higher persistent trophoblast rate compared to open surgery. Long term follow up showed no significant differences in future fertility. If a laparotomy is still necessary, this can be done using a minilaparotomy technique.

The prophylactic use of single shot methotrexate significantly lowers the persistent trophoblast rate. However, the number of women needed to treat with methotrexate is ten to prevent one woman with persistent trophoblast, which seriously questions the usefulness of this strategy. Monitoring serum hCG concentrations seems a better option. The additional use of vasopressin and oxytocin injected in the tube before surgery has no impact on treatment success.

In conclusion, in the surgical management of tubal ectopic pregnancy laparoscopic surgery is a cost effective treatment.

Medical treatment

Drugs studied in the medical treatment of tubal ectopic pregnancy are predominantly methotrexate, and occasionally hyperosmolar glucose and prostaglandins. In view of the side effects of methotrexate as a chemotherapeutic agent, this drug has been compared with prostaglandins and hyperosmolar glucose. Compared to prostaglandins alone or in combination with hyperosmolar glucose, no significant differences are found in treatment success, or in side effects. A trial comparing methotrexate versus hyperosmolar glucose alone was prematurely stopped due to the high failure rate in the hyperosmolar glucose group.

Methotrexate can be administered locally in the tube and systemically. The transvaginal administration of methotrexate under sonographic guidance requires visualization of an ectopic gestational sac and specific skills and expertise of the clinician. This mode of administration is less invasive and more effective than the laparoscopically 'blind' intra-tubal injection, but both modes of administration are less effective than laparoscopic salpingostomy in the elimination of tubal ectopic pregnancy. Moreover, with local methotrexate under laparoscopic guidance the risks of anesthesia and trocar insertion are still present, making laparoscopic surgery the obvious choice of treatment.
Compared to the local routes of administration, systemic methotrexate is practical, easier to administer, and less dependent from clinical skills. In combination with non-invasive diagnostic tools, systemic methotrexate offers the option of a totally non-invasive outpatient management. Therefore, the comparison between systemic methotrexate and laparoscopic salpingostomy is most relevant.

Systemic methotrexate in a fixed multiple dose intramuscular regimen versus laparoscopic salpingostomy did not show significant differences in short and long term medical outcome measures. Health related quality of life was more severely impaired after systemic methotrexate. However, in a case control study, women indicated that they were willing to trade off the increased treatment burden of systemic methotrexate for the benefit of a totally noninvasive management of tubal ectopic pregnancy (Nieuwkerk 1998b). In such a treatment scenario, it was calculated that systemic methotrexate would become less expensive only in women with an initial serum hCG concentration < 1500 IU/l, whereas costs would be similar to laparoscopic salpingostomy in women with an initial serum hCG concentration between 1500 and 3000 IU/l, and higher in women with an initial serum hCG concentration > 3000 IU/l (Mol 1999a).

Methotrexate in one single dose intramuscularly is significantly less effective than laparoscopic salpingostomy. Additional injections for inadequately declining serum hCG concentrations are frequently necessary, resulting eventually in a variable dose regimen. Treatment success of this variable dose regimen is not significantly different compared to laparoscopic salpingostomy in the elimination of tubal ectopic pregnancy. Subgroup analysis again showed that cost savings of this methotrexate regimen are lost in women with an initial serum hCG concentration > 1500 IU/l.

No evidence of a difference was found comparing systemic methotrexate in different dosages: a single dose regimen versus the fixed multiple dose regimen and a lower dose (25 mg/m2) versus the standard dose of 50 mg/m2.

The efficacy of single dose methotrexate is improved by the addition of mifepristone, although a large treatment effect is excluded. The same goes for the addition of traditional Chinese medicine. The experimental finding that methotrexate dissolved in lipiodol suspensions is more effective than methotrexate in saline, as a result of high tissue concentrations and prolongation of the drug effect, has not been implemented in clinical practice.

In conclusion, in the medical treatment of tubal ectopic pregnancy systemic methotrexate can be given in a fixed multiple dose regimen or in a variable dose regimen in women with low initial serum hCG concentrations.
The fixed multiple dose regimen comprises methotrexate 1 mg/kg body weight intramuscularly day 0, 2, 4, 6 alternated with folinic acid 0.1 mg/kg orally day 1, 3, 5, 7 followed by six days without medication. A second course is given on day 14, if the serum hCG concentration on that day is 40% above the initial value on day 0.
A variable dose regimen comprises single shot methotrexate 1 mg/kg body weight or 50 mg/m2 body surface area intramuscularly with an additional methotrexate injection if the serum hCG concentration between day 4 to 7 fails to decline < 15% of the initial value on day 1. If during any successive week of follow-up serum hCG again fails to fall by at least 15%, this results in a repeat injection of methotrexate. After three injections without a serum hCG decline according to the above criterion, surgical treatment is recommended.

The authors of this review feel that the following criteria should be taken into account when considering medical treatment with (systemic) methotrexate for tubal ectopic pregnancy (ASRM 2006):
"pre-treatment testing: serum hCG concentration, complete blood count, liver and renal function tests, type and screen;
"life rules: adequate patient compliance, no use of alcohol, aspirin, NSAID's or fol(in)ic acid supplements, refrain from sexual intercourse, avoidance of sunlight exposure, fluid intake at least 1.5 L daily, 0.9% saline mouthwashes daily and in case of stomatitis 0.12% chlorhexidine mouthwashes;
"follow up: anti D intramuscularly if Rhesus negative, pain relief with paracetamol, serum hCG monitoring until level is undetectable, transvaginal sonography, complete blood counts, liver and renal function tests, delay of pregnancy for at least three months after treatment because of teratogenicity of methotrexate.

Expectant management
The single study comparing systemic methotrexate and expectant management is not informative from a clinical viewpoint. The oral route of administration and the low dosage of methotrexate used in this study (2.5 mg/day during five days) are uncommon and likely to fail. This study virtually represents a comparison between two placebo treatments as is demonstrated in similar success rates of 77% in both treatment groups. Another study -which was stopped prematurely- showed that prostaglandin therapy in selected patients (serum hCG concentration < 2500 IU/l) is significantly better than expectant management without any side effects.

In conclusion, an evaluation of expectant management of tubal ectopic pregnancy can not be adequately made yet.

AUTHORS' CONCLUSIONS

Implications for practice

Laparoscopic surgery is a cost effective treatment in women with tubal ectopic pregnancy. Systemic methotrexate is an alternative nonsurgical treatment option, if the diagnosis of tubal ectopic pregnancy is established noninvasively, thereby offering a complete noninvasive outpatient management.
Systemic methotrexate can only be recommended for hemodynamically stable women with an unruptured tubal ectopic pregnancy and no signs of active bleeding presenting with low initial serum hCG concentrations.

Implications for research

S urgery
Whether a salpingostomy should be done or a salpingectomy is still a matter of debate. The inherent drawbacks of salpingostomy, i.e. the risk of persistent trophoblast and repeat tubal ectopic pregnancy generating additional costs, are only justified if this approach results in a higher spontaneous intrauterine pregnancy rate, thereby saving the treatment burden and costs of subsequent infertility treatment after salpingectomy. A review of cohort studies comparing fertility outcome after salpingostomy and salpingectomy for tubal ectopic pregnancy showed no beneficial effect of conservative surgery on the intrauterine pregnancy rate, whereas the risk of repeat ectopic pregnancy was increased, although not significantly (Clausen 1996; Mol 1996). A retrospective comparative study reporting on life table analysis showed a beneficial effect of salpingostomy as compared to salpingectomy for tubal ectopic pregnancy towards fertility outcome in women with contralateral tubal pathology (Mol 1998a). Whether salpingostomy is beneficial in women without tubal pathology is still unknown. To date, two trials are ongoing comparing salpingostomy versus salpingectomy in these women and the impact on future fertility (Hajenius 1; Fernandez 2).

Medical treatment / expectant management
Further research should focus on dosage schemes of systemic methotrexate, side effects, patients' quality of life and costs.
A study is on the verge of starting comparing methotrexate in a single dose intramuscular regimen versus expectant management in women with a persisting pregnancy of unknown location with plateauing serum hCG concentrations < 2000 IU/l (Hajenius 2). Thus far, this particular subgroup of women, which represents about 10% of women presenting with suspected ectopic pregnancy (Kirk 2006) have been offered medical treatment with methotrexate (Hajenius 1995b; Condous 2004).
Recently, a well designed trial has started that will evaluate expectant management in the treatment of ectopic pregnancy. In a double blinded setting, single dose intramuscular methotrexate is compared with placebo in selected women with an ectopic pregnancy and a serum hCG concentration < 1500 IU/l (Jurkovic).

ACKNOWLEDGEMENTS

The review auhtors would like to thank Mrs Xu Hairong for translating the study of Wang 1998 from Chinese into English language.

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Fernandez 2 *{unpublished data only}*

Randomised controlled trial between conservative versus radical surgical treatment to evaluate subsequent fertility. Ongoing study 08-2004.

Hajenius 1 *{unpublished data only}*

A randomised controlled trial of salpingostomy versus salpingectomy for tubal pregnancy; impact on future fertility. Ongoing study 01-09-2004.

Hajenius 2 *{unpublished data only}*

Randomised controlled trial of systemic MTX in an intramuscular single shot regimen versus expectant management. Ongoing study 01-02-2006.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Alleyassin 2006

Methods	Randomization using sealed envelopes, with block randomization using a computer generated random table Single centre A sample size of 49 women in each group was calculated to find a 21% difference in success rate of single dose and multiple dose treatment (alpha < 0.05 and beta = 0.2) No source of funding stated Ethical committee approval Published as full paper
Participants	Hemodynamically stable women with a tubal mass < 3.5 cm in diameter on transvaginal sonography with absence of fetal heart beat and serum hCG < 15,000 IU/l and fear of patient future infertility Number of women randomized: 108 The trial was carried out at Dr. Shariati Hospital Tehran, Iran between September 23, 2003 to March 21, 2005
Interventions	Single dose systemic MTX 50 mg/m2 IM versus multiple dose systemic MTX 1.0 mg/kg IM on days 0,2,4,6 alternated folinic acid 0.1 mg/kg oral on days 1,3,5,7
Outcomes	Treatment success method of diagnosis: complete elimination of the ectopic pregnancy (serum hCG < 15 IU/L) Persistent trophoblast method of diagnosis: in the single dose group if the serum hCG concentration on day 7 did not decrease by 15% after one week of treatment or serum hCG not < 15 IU/l after 6 weeks of treatment. In the multiple dose group if the serum hCG concentration did not decrease by 15% in 48 hours or serum hCG not < 15 IU/l after 6 weeks of treatment. Persistent trophoblast was treated with single dose systemic MTX. Need for surgery

Alleyassin 2006 *(Continued)*

	hCG clearance time method of diagnosis: the mean number of days to reach serum hCG concentrations < 15 IU/l Complications method of diagnosis: MTX related side effects were recorded
Notes	Ectopic pregnancy was diagnosed if serum hCG > 1800 IU/l and no viable intra uterine pregnancy was evident and if the serum hCG concentration was < 1800 IU/l but plateau ing or < 50% increase over 48 hours

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Cohen 1996

Methods	Randomization using computer generated random number tables Single centre No power calculation No source of funding stated Ethical committee approval not stated Published as full paper
Participants	Clinically stable women with an ectopic pregnancy (< 3.5 cm) with rising serum hCG concentrations Number of women randomized: 20 The trial was carried out at the McGill University, Cleveland, Ohio, USA Timing and duration of the trial not stated
Interventions	MTX 1 mg/kg transvaginally under sonographic guidance versus systemic MTX single dose 50 mg/m2 IM
Outcomes	Treatment success method of diagnosis: an uneventful decline of serum hCG to undetectable levels (< 12 IU/l) Treatment failure method of diagnosis: a subsequent necessary surgical intervention for abdominal pain Persistent trophoblast method of diagnosis: a second methotrexate injection by the same route as the initial one for a serum hCG decline < 15% or a rise between days 4 and 7, or a plateau between the weekly levels hCG resolution time method of diagnosis: mean number of days for serum hCG to become < 12 IU/L Ectopic mass resolution time method of diagnosis: mean number of days for the ectopic mass to become undetectable on transvaginal sonography Side effects method of diagnosis: not clearly stated, i.e.. follow-up of blood counts and liver enzymes

Cohen 1996 *(Continued)*

	Serum MTX levels method of diagnosis: not stated Pregnancy outcome method of diagnosis: occurrence of pregnancy, follow-up not stated
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Dias Pereira 1999

Methods	Randomization by a computer program with block randomization, with stratification for pre-existing tubal pathology and initial serum hCG concentration. Randomization was done before a confirmation laparoscopy. Multi centre Tubal patency rate after laparoscopic salpingostomy was assumed to be 80%. A sample size of 100 patients would allow to detect a difference in tubal patency rate, in favour of systemic methotrexate, of 18%, with a two-sided chi square test at p = 0.05 and with a power of 80% Funding by the Health Insurance Funds Council, Amstelveen, The Netherlands Ethical committee approval Intention to treat analysis Published as letter to the editor
Participants	Hemodynamically stable women with a laparoscopically confirmed unruptured tubal pregnancy without fetal cardiac activity and no signs of active bleeding, no contraindications to receiving systemic MTX, (leucopenia, thrombocytopenia, or high concentrations of liver enzymes or serum creatinine) or contraindications to laparoscopic surgery, (documented extensive pelvic adhesions, large fibroid uterus, and severe ovarian hyperstimulation syndrome) Number of women randomized: 74 Number of women originally randomized 140 Secondary exclusions for non tubal pregnancy, tubal rupture, and/or active bleeding: 40 Lost to follow-up: 10 No desire for future pregnancy: 16 The trial took place in six Dutch hospitals: the Academic Medical Centre of the University of Amsterdam, the Onze Lieve Vrouwe Gasthuis and the University Hospital Free University in Amsterdam and the University Hospitals of Groningen, Nijmegen and Utrecht, The Netherlands between January 1, 1994 and September 1, 1996
Interventions	Systemic MTX 1.0 mg/kg IM on days 0,2,4,6 alternated folinic acid 0.1 mg/kg oral on days 1,3,5,7 versus laparoscopic salpingostomy
Outcomes	Fertility outcome method of diagnosis: cumulative frequency and pregnancy outcome of first subsequent pregnancy by means of telephonic contacts or questionnaires

Dias Pereira 1999 *(Continued)*

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Egarter 1991

Methods	Randomization during laparoscopy, method not stated Single centre Interim analysis was planned in order to stop the study as soon as a statistical trend for any of the groups could be demonstrated. It was estimated that a sample of about 20 patients per group would be required Funding by the Medizininisch Wissenschaftlicher Fonds der Bürgermeisters der Bundeshauptstadt Wien and by the Japan Society for the Promotion of Science Ethical committee approval Published as full paper
Participants	Women with a laparoscopically confirmed unruptured tubal pregnancy without active bleeding and a serum hCG concentration < 2,500 IU/l Number of women randomized: 23 The trial was carried out at the I Univ Frauenklinik, Vienna, Austria Timing and duration of the trial not stated
Interventions	10 mg PGF2 alpha in 1.5-2 ml into the tubal pregnancy + 25 mg conjugated estrogens injected into the ipsilateral ovary under laparoscopic guidance + 500 mg synthetic PGE2 derivative IM twice daily during the first 3 postoperative days versus 1.5-2 ml isotonic NaCl solution injected into the tubal pregnancy under laparoscopic guidance versus no medical therapy at all
Outcomes	Treatment success method of diagnosis: an uneventful decline of serum hCG to undetectable levels Treatment failure method of diagnosis: a subsequent surgical intervention with removal of the tubal pregnancy for post-operatively rising serum hCG concentrations and/or increase in clinical/abdominal symptoms Hospitalization time method of diagnosis: number of days in the hospital Side effects method of diagnosis: not stated
Notes	If possible, all women were released from the hospital on the second postoperative day

Risk of bias

Bias	Authors' judgement	Support for judgement

Egarter 1991 *(Continued)*

Allocation concealment?	Unclear risk	B - Unclear

El-Sherbiny 2003

Methods	Method of randomization by computer Multi centre No power calculation No source of funding stated No ethical committee approval Published as full paper
Participants	hemodynamically stable patients with confirmed diagnosis of unruptured tubal pregnancy < 4 cm without fetal cardiac activity and a serum hCG < 10,000 IU/l and no contraindications for laparoscopic surgery or MTX (elevated serum liver enzymes, creatinine > 1.3 mg/dl, WBCs < 3,000/mm3 and platelets < 50,000/mm3) and desire for future pregnancy Number of women initially randomized: 55 The trial was carried out at two governmental hospitals (Damietta General Hospital and El Mataria Teaching Hospital in Cairo) and two private hospitals (El-Sherbiny Hospital in Damietta and Mera Center in El Mansoura) in Egypt between February 1996 trough July 2001
Interventions	Single dose systemic MTX (50 mg/m2) versus laparoscopic surgery
Outcomes	Treatment success method of diagnosis: an uneventful decline of serum hCG to undetectable levels (< 5 IU/l) Tubal patency method of diagnosis: by hysterosalpingogram 3-6 months post treatment Persistent trophoblast method of diagnosis: < 50% fall of initial level in serum hCG by day 7 or 90% by day 12, or started to plateau or rise thereafter Fertility outcome method of diagnosis: intra uterine pregnancy and repeat ectopic pregnancy within one year post treatment follow up
Notes	The authors were contacted by e-mail for further information on the trial. In all centres a non-laparoscopic diagnostic algorithm was followed to diagnose tubal ectopic pregnancy Salpingostomy was performed unless there was an indication for salpingectomy (n=8), i.e. uncontrollable post salpingostomy bleeding (n=2), tubal rupture (n=1), severe peritubal adhesions (n=2), or recurrent ectopic pregnancy in the same tube on patients request (n=3). Persistent trophoblast was treated with 50 mg/m2 MTX orally Pregnancy was allowed after 3 months Women who did not conceive were offered an hysterosalpingogram post ectopic treatment
Risk of bias	

El-Sherbiny 2003 *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Elmoghazy 2000

Methods	Method of randomization not stated Single centre No power calculation Source of funding not stated Ethical committee approval not stated Published as abstract
Participants	All women with early diagnosed tubal pregnancy who underwent surgical conservation of the tube Number of women randomized: 47 The trial was carried out El-Minia University in Egypt Timing and duration of the trial not stated
Interventions	Conservative surgery of the tube and a single dose of MTX postoperatively (1 mg/kg IM) within 24 hours versus conservative surgery alone
Outcomes	Treatment success method of diagnosis: an uneventful decline of serum hCG to undetectable levels (< 15 IU/l) Persistent trophoblast method of diagnosis: a rise or plateau of serum hCG concentration postoperatively or an inadequate decline (< 20% between two consecutive measurements taken seven days apart) Side effects method of diagnosis: recording of any complication related to MTX and measurement of complete blood picture, liver and kidney functions before and one week after MTX dose
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Fedele 1998

Methods	Randomization by telephone using a computer generated list before salpingotomy Multi centre No power calculation Source of funding not stated

Fedele 1998 *(Continued)*

	Ethical committee approval Published as full paper
Participants	Women with a laparoscopically confirmed unruptured tubal pregnancy < 5 cm without adhesions involving the salpinx Number of women randomized: 25 The trial took place at the University of Verona, the University of Milano, and Ospedale di Gallarate, Gallerate, Italy, between October 1995 and June, 1997
Interventions	Laparoscopic salpingotomy with intra mesosalpingeal injection of 20 IU oxytocin diluted in 20 ml saline versus laparoscopic salpingotomy with intra mesosalpingeal injection of 20 ml saline alone
Outcomes	Treatment success method of diagnosis: conversion to salpingectomy Bleeding during salpingotomy method of diagnosis: by means of an assessment form using scores 1 to 3 1. minimal, 2. moderate, 3. abundant Removal of the pregnancy method of diagnosis: by means of an assessment form using scores 1 to 3 1. easy, 2. moderately difficult, 3. difficult Bleeding at the site of the pregnancy method of diagnosis: by means of an assessment form using scores 1 to 3 1. minimal, 2. moderate, 3. abundant
Notes	The decision to perform salpingotomy was made by the surgeon on the basis of an overall clinical assessment (age, obstetric history, desire for children and general conditions) and intraoperative findings (non ruptured tube, size < 5 cm, absence of adhesions involving the salpinx, and conditions of the contralateral tube) The surgeons were not blinded for the intervention

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Fernandez 1991

Methods	Randomization using a random number table Single centre No power calculation No source of funding stated Ethical committee approval Published as full paper
Participants	Women with a transvaginal sonographic finding of a gestational sac in the fallopian tube with an empty uterus, and no evidence of fluid in the pouch of Douglas, and without abdominal pain

Fernandez 1991 *(Continued)*

	Number of women randomized: 21 The trial was carried out at the Hôpital Antoine Béclère, Clamart, France between April 1, 1989 and December 31, 1989
Interventions	MTX 1mg/kg transvaginally under sonographic guidance on day 1 combined with systemic MTX 1mg/kg IM on days 3,5,7 alternated with folinic acid 0.1 mg/kg IM on days 2,4,6,8 versus Sulprostone 500 mg transvaginally under sonographic guidance on day 1, combined with 500 mg IM on days 2,3
Outcomes	Treatment success method of diagnosis: an uneventful decline of serum hCG to undetectable levels (< 10 IU/l) Treatment success analyzed from initial hCG level method of diagnosis: initial serum hCG level < 1000 IU/l versus 1000-5000 IU/l versus > 5000 IU/l Treatment failure method of diagnosis: operative re intervention (laparoscopy) for the occurrence of abdominal pain or rising serum hCG concentrations hCG resolution time method of diagnosis: mean number of days for serum hCG to become < 10 IU/l Hospitalization time method of diagnosis: number of days in the hospital Side effects method of diagnosis: complete blood count, liver and kidney function test monitored twice weekly Tubal patency method of diagnosis: by hysterosalpingogram 2 months after the first menstruation Pregnancy outcome method of diagnosis: recording desire for pregnancy and occurrence and outcome of pregnancy, follow-up > 6 months
Notes	Before injecting medical therapy the tubal content was aspirated and 2.5 cm3 volume of both drugs was administered into the ectopic sac Women were discharged from the hospital when serum hCG levels dropped below 30% of preoperative level, excluding the women treated on an outpatient basis

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Fernandez 1994

Methods	Randomization by blinded computer generated random number tables Single centre No power calculation No source of funding stated Ethical committee approval Published as full paper

Fernandez 1994 *(Continued)*

Participants	Women with an unruptured ectopic pregnancy clearly visualized by transvaginal sonography and a predictive therapeutic score < 14 Number of women randomized: 48 The trial was carried out at the Hôpital Antoine Béclère, Clamart, France between July and October 1991
Interventions	MTX 1 mg/kg injected transvaginally under sonographic guidance combined with systemic MTX 1 mg/kg IM after 48 hours versus MTX 1 mg/kg transvaginally under sonographic guidance versus MTX 0.5 mg/kg transvaginally under sonographic guidance versus systemic single dose MTX 1 mg/kg IM
Outcomes	Treatment success method of diagnosis: an uneventful decline of serum hCG to undetectable levels (< 10 IU/l) by primary treatment Treatment failure method of diagnosis: an operative re intervention for the occurrence of unusual abdominal pain or an inadequate decrease of serum hCG (40% above the hCG values observed on the normal regression curve 10 days after initial MTX administration) Persistent trophoblast method of diagnosis: additional systemic MTX injections IM for serum hCG concentrations 20% above the hCG values observed on the normal regression curve 10 days after initial MTX administration hCG resolution time method of diagnosis: number of days for serum hCG to become < 10 IU/l Side effects method of diagnosis: occurrence of stomatitis, complete blood count and renal and liver function tests at days 2 and 15 after MTX administration MTX plasma levels (fluorescent polarization immuno assay) and pharmacokinetic parameters i.e.. terminal phase rate constant, terminal half life, area under the curve, mean residence time, time to maximal concentration, maximal concentration and minimal concentration after 48 hours method of diagnosis: venous blood samples at 0.25, 0.5, 1, 2, 6, 12, 24, 36, 48 hours after MTX administration
Notes	Pre therapeutic predictive score are six criteria graded on the scale from 1 to 3; gestational age, serum hCG level, serum progesterone level, existence of abdominal pain, ultrasound evaluation of hemoperitoneum volume, and heamatosalpinx diameter Before injecting medical therapy the tubal content was aspirated

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Fernandez 1995

Methods	Randomization using a random number table Single scienter No power calculation No source of funding stated

Fernandez 1995 *(Continued)*

	Ethical committee approval Published as full paper
Participants	All women with ectopic pregnancy visualized by transvaginal sonography with a pre therapeutic score < 13, and no suspicion of rupture or liver or kidney diseases and/or abnormal laboratory parameters with elevated liver enzymes or neutropenia that contraindicated MTX treatment Number of women randomized: 40 The trial was carried out at the Hôpital Antoine Béclère, Clamart, France between September 1, 1992 and October 1, 1993
Interventions	MTX 1 mg/kg transvaginally under sonographic guidance versus laparoscopic salpingostomy
Outcomes	Treatment success method of diagnosis: an uneventful decline of serum hCG to undetectable levels (< 10 IU/l) by primary treatment Treatment failure method of diagnosis: additional injection of systemic MTX IM or surgical reintervention for persistence of high serum hCG concentrations, or the occurrence of abdominal pain hCG resolution time method of diagnosis: mean number of days for serum hCG to become < 10 IU/l Hospitalization time method of diagnosis: number of postoperative days in the hospital Side effects method of diagnosis: liver function test and red and white cell counts on day 10 Tubal patency method of diagnosis: by hysterosalpingogram 2 months after the first menstrual period Pregnancy outcome method of diagnosis: recording desire for pregnancy and occurrence and outcome of pregnancy by personal or telephonic contact, follow-up > 6 months
Notes	Part of the results are updated in the study of Fernandez 1998 Pre therapeutic predictive score are six criteria graded on the scale from 1 to 3; gestational age, serum hCG level, serum progesterone level, existence of abdominal pain, ultrasound evaluation of hemoperitoneum volume, and heamatosalpinx diameter Before injecting medical therapy the tubal content was aspirated In the MTX group women were monitored on an outpatient basis, unless they lived too far of the hospital. In the laparoscopy group women were hospitalized for 2 days as is usual in France

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Fernandez 1998

Methods	Randomization using a random number table

Fernandez 1998 *(Continued)*

	Single centre No power calculation No source of funding stated Ethical committee approval Published as full paper
Participants	All women with ectopic pregnancy visualized by transvaginal or transabdominal sonography with a pre therapeutic score < 13, and no suspicion of rupture or liver or kidney diseases and/or abnormal laboratory parameters with elevated liver enzymes or neutropenia that contraindicated MTX treatment Number of women randomized: 100 Lost to follow up: 18 No desire for pregnancy: 26 The trial was carried out at the Hôpital Antoine Béclère, Clamart, France between September 1, 1992 and October 1, 1995
Interventions	MTX 1 mg/kg transvaginally under sonographic guidance versus laparoscopic salpingostomy and systemic single dose MTX 1 mg/kg IM (in women whose ectopic pregnancy could not be safely or easily punctured) versus laparoscopic salpingostomy
Outcomes	Treatment success method of diagnosis: an uneventful decline of serum hCG to undetectable levels (< 10 IU/l) by primary treatment Tubal preservation method of diagnosis: tubal preservation after primary treatment plus any additional conservative therapeutic interventions Treatment failure method of diagnosis: additional injection of systemic MTX IM or surgical re intervention for persistence of high serum hCG concentrations, or the occurrence of abdominal pain or both hCG resolution time method of diagnosis: mean number of days for serum hCG to become < 10 IU/l Hospitalization time method of diagnosis: number of postoperative days in the hospital Pregnancy outcome method of diagnosis: recording desire for pregnancy and occurrence and outcome of pregnancy by personal or telephonic contact, follow-up > 1 year
Notes	Results have been reported earlier for 40 women (20 treated by local MTX under sonographic guidance and 20 by laparoscopic salpingostomy) in the study of Fernandez 1995 Pre therapeutic predictive score are six criteria graded on the scale from 1 to 3; gestational age, serum hCG level, serum progesterone level, existence of abdominal pain, ultrasound evaluation of hemoperitoneum volume, and heamatosalpinx diameter In the MTX group women were monitored on an outpatient basis, unless they lived too far of the hospital or the procedure was preformed after 16.00 hours. In the laparoscopy group women were hospitalized for 2 days as is recommended in France and reimbursed by the French national health insurance system.

Risk of bias

Bias	Authors' judgement	Support for judgement

Fernandez 1998 *(Continued)*

Allocation concealment?	Unclear risk	B - Unclear

Fujishita 1995b

Methods	Method of randomization not stated Single centre No power calculation No source of funding stated Ethical committee approval not stated Published as full paper
Participants	All women with desire for future pregnancy with an unruptured ectopic pregnancy (< 5 cm), estimated blood loss into the peritoneal cavity < 500 ml, no active bleeding, and no fetal cardiac activity Number of women randomized: 26 The trial was carried out at the Nagasaki University School of Medicine, Nagasaki, Japan between May 1991 to July 1993
Interventions	MTX 20-50 mg dissolved in 2 ml physiological saline versus MTX 20-50 mg dissolved in 2 ml lipiodol with phosphatidylcholine both under laparoscopic guidance
Outcomes	Treatment success method of diagnosis: an uneventful decline of urine and serum hCG to undetectable levels (< 2 IU/l) Treatment failure method of diagnosis: rupture Persistent trophoblast method of diagnosis: additional systemic MTX 20 mg IM for 4 days for a rise or less than smoothly decline in serum hCG hCG resolution time method of diagnosis: mean number of days for urine hCG and serum hCG to become < 2 IU/l Complications method of diagnosis: not stated Tubal patency method of diagnosis:by hysterosalpingogram 3 months after initial treatment Pregnancy outcome method of diagnosis: recording desire for pregnancy and occurrence and outcome of pregnancy, follow-up 6-31 months
Notes	MTX dose in first four women 20 mg, remaining women 50 mg In one woman MTX suspension was administered transvaginally under sonographic guidance

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	B - Unclear

Fujishita 2004

Methods	Method of randomization by computer generated randomization list Single centre 50 patients were needed to reduce the adhesion rate from 50% after salpingotomy with suturing to 25% in the non suturing group No source of funding stated Ethical committee approval Published as full paper
Participants	Hemodynamically stable women with a tubal pregnancy without signs of active bleeding and no severe adhesions in the tubal wall in whom successful salpingotomy was performed Number of women randomized: 75 Number of patients for second look laparoscopy: 38 Lost to follow up: 9 Desire for pregnancy: 22 The trial was carried out at Nagasaki University School of Medicine, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan between May 1996 to December 2002
Interventions	Salpingotomy without tubal suturing versus salpingotomy with tubal suturing
Outcomes	Treatment success method of diagnosis: an uneventful decline of serum hCG to undetectable levels Persistent trophoblast method of diagnosis: uneventful decline of serum hCG for which additional MTX (20 mg IM for 4 days) was installed Operation time: method of diagnosis; mean operation time in minutes Tubal patency method of diagnosis: number of patent ipsilateral tubes at second look laparoscopy by chromopertubation Peritubal adhesion rate method of diagnosis: degree of ipsilateral adhesions conform the American Fertility Society classification 1998 at second look laparoscopy Tubal fistula Method of diagnosis: at second look laparoscopy Reproductive performance method of diagnosis: (cumulative) intrauterine (viable fetus) and ectopic pregnancy rate after 6-65 months
Notes	The authors were contacted to provide more data on persistent trophoblast and how this was treated and on the number of women with spontaneous pregnancies. Surgery was performed by laparoscopy Tubal suturing was performed by closing the incision in one layer by one or two interrupted sutures using absorbable stiches Second look laparoscopy was performed 3 months after the initial operation

Fujishita 2004 *(Continued)*

	The authors included pregnancies that were the result of IVF-ET

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Gazvani 1998

Methods	Randomization by consecutively numbered envelopes. A computer generated randomization sequence was used. Randomization was done after a confirmation laparoscopy. Single centre Sample size was not based on prespecified power calculations as this study was a feasibility study. The aim was to recruit all eligible women in a 24 month period No source of funding stated Ethical committee approval not stated Intention to treat analysis Published as full paper
Participants	Hemodynamically stable women with a laparoscopically confirmed unruptured tubal pregnancy without active bleeding from the fimbrial end, < 4 cm on transvaginal sonography, no contraindications to receiving systemic MTX (hepatic or renal dysfunction, haemorrhagic disorders or women on anticoagulant therapy, long term corticosteroid users, smokers > 35 years) Number of women randomised: 50 The trial took place at the Early Pregnancy Unit at Singleton Hospital, Swansea, United Kingdom between April 1994 and April 1996
Interventions	Single dose systemic MTX (50 mg/m2 IM) alone versus the same regimen in combination with mifepristone 600 mg orally
Outcomes	Treatment success method of diagnosis: complete elimination of the ectopic pregnancy (serum hCG < 12 IU/L) by primary treatment Persistent trophoblast method of diagnosis: if the serum hCG concentration on day 7 did not decrease by 15% as compared to the value on day 4. Persistent trophoblast was treated with single dose systemic MTX (50 mg/m2 im). Tubal preservation method of diagnosis: tubal preservation after primary treatment plus any additional conservative therapeutic interventions hCG clearance time method of diagnosis: the median number of days to reach serum hCG concentrations < 12 IU/l Side effects and complications method of diagnosis: follow-up of complete blood counts, liver and renal function tests Tubal patency method of diagnosis: by hysterosalpingography performed after complete resolution of the ectopic pregnancy and following a first normal period

Gazvani 1998 *(Continued)*

	Overall tubal patency method of diagnosis: tubal patency including those patients who underwent salpingectomy
Notes	Peritoneal lavage was carried out at confirmation laparoscopy

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Gjelland 1995

Methods	Method of randomization not stated Single centre No power calculation No source of funding stated Ethical committee approval Published as full paper
Participants	Women with an ectopic pregnancy (< 4 cm) on transvaginal ultrasound and serum hCG concentration < 3,000 IU/l, and little or no intraabdominal bleeding Number of women randomized: 80 The trial was carried out at Haukeland University Hospital, Bergen, Norway between September 1991 and January 1994
Interventions	Hyperosmolar glucose 50% 10-20 ml transvaginally under sonographic guidance versus hyperosmolar glucose 50% 10-20 ml under laparoscopic guidance
Outcomes	Treatment success method of diagnosis: an uneventful decline of serum hCG to undetectable levels (< 5 IU/l) Treatment failure method of diagnosis: transvaginal sonography group: second injection for persistent trophoblast and/or surgical re intervention after second glucose injection laparoscopy group: conversion to laparotomy for technical difficulties related to substandard laparoscopic equipment and poor training, and for intraabdominal adhesions or surgical re intervention for an increase in serum hCG Persistent trophoblast method of diagnosis: transvaginal sonography group: second injection for an increase of serum hCG hCG resolution time method of diagnosis: mean number of days for serum hCG to become < 5 IU/l in the successfully treated group Hospital stay method of diagnosis: number of days in the hospital, analyzed for both successfully and unsuccessfully treated women Tubal patency method of diagnosis: by hysterosalpingogram at least 4 months after treatment

Gjelland 1995 *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Graczykowski 1997

Methods	Method of randomization by drawing cards Single centre No power calculation Funding in part by National Institutes of Health grant to GCRC M01 RR-43, Betheseda, Maryland, USA Ethical committee approval Published as full paper
Participants	All women who underwent (laparoscopic) salpingostomy for tubal ectopic pregnancy without signs of severe anemia (WBC < 4000/ml, hematocrit < 26%), signs of active liver disease (bilirubin > 1.2 mg/dl, SGOT/SGPT > 70 IU/dl) or signs of kidney disease (serum creatinine > 1.4 mg/dl), leukemia, bone marrow abnormalities, or allergy to MTX Number of women randomised: 129 Lost to follow-up: 13 The trial was carried out at Los Angeles County and University of Southern California Medical Centre, USA between July 1993 and March 1995
Interventions	Salpingostomy and a single dose of MTX postoperatively (1 mg/kg IM) within 24 hours versus salpingostomy alone
Outcomes	Treatment success method of diagnosis: an uneventful decline of serum hCG to undetectable levels (< 15 IU/l) Persistent trophoblast method of diagnosis: increase of serum hCG concentration postoperatively or an inadequate decline (< 20% between two consecutive measurements taken three days apart) hCG resolution time method of diagnosis: mean number of days for serum hCG to become undetectable (< 15 mIU/ml) Side effects method of diagnosis: questionnaire about any symptoms and possible side effects related to the medication and measurement of complete blood count, bilirubin, and SGOT/SGPT
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	C - Inadequate

Gray 1995

Methods	Randomization during laparoscopy by sealed envelopes, stratification into 6 subgroups based on age and an existing risk scoring scheme Single centre No power calculation Funding by Swedish Medical Research Council and by the Göteborg Medical Society Göteborg, Sweden Ethical committee approval Published as full paper
Participants	Hemodynamically stable women with a laparoscopically confirmed tubal pregnancy (< 4 cm) and serum hCG concentrations < 10,000 IU/l (if known at the time of randomization). Women with a tubal pregnancy < 1 cm and serum hCG concentration < 1,000 IU/l were excluded as were women in whom the tubal pregnancy was not anatomically accessible for laparoscopic removal Number of women randomized: 109 The trial was carried out at Sahlgrenska University Hospital, Göteburg, Sweden between May 1, 1987 and June 30, 1989
Interventions	Laparoscopy versus laparotomy
Outcomes	Treatment success method of diagnosis: elimination of trophoblastic activity documented by a fall in serum hCG to non-pregnant levels (< 20 IU/l) beyond postoperative day 7 Treatment failure method of diagnosis: medical or surgical interventions for elimination of residual trophoblastic activity. Operative complications that required surgical intervention or inpatient observation were analyzed separately Total costs of care method of diagnosis: multiplying the unit cost by each type of care by the number of units used Cost effectiveness method of diagnosis: effectiveness of the surgical strategies including additional interventions of follow-up, relative to the costs incurred Sensitivity and threshold analyses method of diagnosis: changing key baseline assumptions about clinical outcomes and patterns of care
Notes	Surgery was planned between 08.00 and 17.00 h Monday to Friday when at least two of five laparoscopic surgeons were on duty Risk scoring scheme: previous ectopic pregnancy, IUCD in situ, history of infertility, previous abdominal surgery, age < 27, 27-31, > 31 years Unless salpingectomy was otherwise indicated, all laparoscopy and laparotomy procedures were planned as tube sparing linear salpingotomy Health care resources: hospital bed use from day of surgery onwards, investigation of incidental findings made during ectopic pregnancy surgery, hospital, physician, and laboratory costs for follow-up and repeat hospital stay Types of care: duration of surgeons operation, duration of diagnostic laparoscopy and randomization, duration of therapeutic portion procedure, duration of total theatre time, duration of postoperative stay in recovery room,women requiring transfusions, postoperative length of stay, women requiring second medical/surgical intervention for persistent trophoblast, women readmitted for postoperative

Gray 1995 *(Continued)*

	abdominal pain, number of postoperative outpatient gynecology visits/patient, number of follow-up ultrasounds, duration of follow-up Costs were based on total costs instead of fixed (overhead) versus variable (volume dependant) costs estimated with data between November 1992 and March 1993 from Huddinge University Hospital/ Karolinska Institute Stockholm, Sweden

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Hajenius 1997

Methods	Randomization by a computer program with block randomization, with stratification for pre-existing tubal pathology and initial serum hCG concentration. Randomization was done before a confirmation laparoscopy Multi centre Tubal patency rate after laparoscopic salpingostomy was assumed to be 80%. A sample size of 100 women would allow to detect a difference in tubal patency rate, in favour of systemic methotrexate, of 18%, with a two-sided chi square test at p = 0.05 and with a power of 80% Funding by the Health Insurance Funds Council, Amstelveen, The Netherlands Ethical committee approval Intention to treat analysis Published as full paper
Participants	Hemodynamically stable women with a laparoscopically confirmed unruptured tubal pregnancy without fetal cardiac activity and no signs of active bleeding, no contraindications to receiving systemic MTX, (leucopenia, thrombocytopenia, or high concentrations of liver enzymes or serum creatinine) or contraindications to laparoscopic surgery, (documented extensive pelvic adhesions, large fibroid uterus, and severe ovarian hyperstimulation syndrome) Number of women randomised: 100 Number of women originally randomised 140 Secondary exclusions for non tubal pregnancy, tubal rupture, and/or active bleeding: 40 The trial took place in six Dutch hospitals: the Academic Medical Centre of the University of Amsterdam, the Onze Lieve Vrouwe Gasthuis and the University Hospital Free University in Amsterdam and the University Hospitals of Groningen, Nijmegen and Utrecht, The Netherlands between January 1, 1994 and September 1, 1996
Interventions	Systemic MTX 1.0 mg/kg IM on days 0,2,4,6 alternated folinic acid 0.1 mg/kg oral on days 1,3,5,7 versus laparoscopic salpingostomy
Outcomes	Treatment success method of diagnosis: complete elimination of the tubal pregnancy (serum hCG < 2 IU/L) and preservation of the tube by primary treatment Persistent trophoblast method of diagnosis: in patients treated with systemic MTX, by a serum hCG concentration above 40% of the initial value on day 14. In patients treated by salpingostomy, by rising or plateau ing serum hCG concentrations. In both treatment groups persistent trophoblast was treated with systemic MTX.

Hajenius 1997 *(Continued)*

	Tubal preservation method of diagnosis: tubal preservation after primary treatment plus any additional conservative therapeutic interventions hCG clearance time method of diagnosis: the median number of days to reach undetectable serum hCG levels Side effects and complications method of diagnosis: follow-up of complete blood counts, liver and renal function tests to detect MTX toxicity and anaesthesia effects Tubal patency method of diagnosis: by hysterosalpingography performed three months after completion of treatment Overall tubal patency method of diagnosis: tubal patency including those patients who underwent salpingectomy
Notes	Pre-existing tubal pathology was defined as previous ectopic pregnancy, previous tubal surgery, previous pelvic inflammatory disease, or proven tubal pathology by hysterosalpingography or laparoscopy In women with persistent bleeding from the tube after removal of the trophoblastic tissue by laparoscopic salpingostomy, bleeding points were identified and controlled with bipolar coagulation, with an effort not to damage the tubal mucosa. If still unsuccessful a salpingectomy was performed either by laparoscopy or by laparotomy

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Hordnes 1997

Methods	Method of randomization not stated Single centre No power calculation No source of funding stated Ethical committee approval Published as full paper
Participants	Women with an ectopic pregnancy (< 4 cm) on transvaginal sonography and a serum hCG concentration < 3,000 IU/l and little or no intraabdominal bleeding Number of women randomized: 80 The trial was carried out at Haukeland University Hospital, Bergen, Norway between September 1991 and January 1994
Interventions	Hyperosmolar glucose 50% 10-20 ml transvaginally under sonographic guidance versus hyperosmolar glucose 50% 10-20 ml under laparoscopic guidance
Outcomes	Fertility outcome method of diagnosis: pregnancy rates and pregnancy outcome in successfully treated women trying to conceive, contacted by a questionnaire 23-51 months after treatment

Hordnes 1997 *(Continued)*

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Klauser 2005

Methods	Method of randomization not stated Single centre No power calculation No source of funding stated Ethical committee approval Published as abstract
Participants	Women with a clinical diagnosis of an unruptured ectopic pregnancy (upper limit serum hCG concentration 10,000 IU/l) Number of women randomized: 51 The trial was carried out at University of Mississippi Medical Centre, Jackson, MS, USA
Interventions	Single dose MTX (50 mg/m2) versus multiple dose MTX (1 mg/kg on day 1,3,5)
Outcomes	Treatment success method of diagnosis: an uneventful decline of serum hCG to undetectable levels (< 5 IU/l) Need for surgery Side effects serum hCG resolution time method of diagnosis: number of days for serum hCG to become < 5 IU/l
Notes	Not mentioned if leucovorin was given on alternating days (day 2,4,6)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Korhonen 1996

Methods	Randomization was done in the hospital pharmacy using a table of random numbers. The code was opened after the end of treatment of the last patient Double blind, placebo controlled study, single centre

Korhonen 1996 *(Continued)*

	A trial of 58 women had an 80% chance of detecting a statistically significant difference of 30% between rates of recovery without laparoscopy No source of funding stated Ethical committee approval Published as full paper
Participants	Women with an ectopic pregnancy (< 4 cm) and a serum hCG concentration < 5,000 IU/l with no or mild abdominal pain. Patients with a rise in serum hCG > 50% in 2 days were excluded Number of women randomised: 60 The trial was carried out at Helsinki University Central Hospital, Finland during a 3 year period
Interventions	Systemic MTX 2.5 mg/day orally during 5 days versus expectant management
Outcomes	Treatment success method of diagnosis: an uneventful decline of serum hCG to undetectable levels (< 5 IU/l) Treatment failure method of diagnosis: a laparoscopic intervention for rising or plateau ing serum hCG concentrations and/or for severe clinical symptoms, i.e.. increasing abdominal pain or signs of intraabdominal haemorrhage on transvaginal sonography hCG resolution time method of diagnosis: number of days for serum hCG to become < 5 IU/l
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

Landstrom 1998

Methods	Method of randomization not stated Multi centre No power calculation No source of funding stated Ethical committee approval not stated Published as abstract
Participants	Hemodynamically stable women with a tubal pregnancy at diagnostic laparoscopy and a serum hCG concentration < 3,000 IU/l Number of women randomized: 31 The trial took place in the following Swedish hospitals: Sahlgrenska University, Gotenborg, Ostersund Hospital, Sodertalje Hospital, Karlskrona Hospital, University Hospital Malmo and Akademiska University Hospital Uppsala, Sweden. Timing and duration of the trial not stated

Landstrom 1998 *(Continued)*

Interventions	Systemic MTX in a oral regimen versus prostaglandins F2a and hyperosmolar glucose under laparoscopic guidance
Outcomes	Treatment success method of diagnosis: complete elimination of the tubal pregnancy and preservation of the tube by primary treatment Postoperative abdominal pain and vaginal bleeding method of diagnosis:abdominal pain and vaginal bleeding after treatment as indicated by the women in a questionnaire
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Lang 1990

Methods	Randomization by computer Single centre No power calculation No source of funding stated Ethical committee approval Published as full paper
Participants	Hemodynamically stable women with a laparoscopically confirmed unruptured tubal pregnancy without active bleeding, and a urinary hCG concentration < 5,000 IU/l Number of women randomized: 31 The trial was carried out at the University of Graz, Austria, during a 9 month period
Interventions	Prostaglandin F2a 7.5-10 mg in 1.5-2.0 ml solvent injected in the gestational sac and 25 mg conjugated oestrogen injected in the corpus luteum of the ipsilateral ovary under laparoscopic guidance combined with systemic Prostaglandin-E2 derivative 500 mg IM on the first 2 postoperative days versus hyperosmolar glucose 10-20 ml 50% under laparoscopic guidance
Outcomes	Treatment success method of diagnosis: an uneventful decline of serum hCG to undetectable levels (< 5 IU/l) Treatment failure method of diagnosis: surgical intervention for increasing or plateau ing hCG levels and clinical signs of imminent tubal rupture hCG resolution time method of diagnosis: number of days for urinary hCG and serum hCG to become undetectable (< 5 IU/l) Hospitalisation time method of diagnosis: number of days in the hospital Side effects

Lang 1990 *(Continued)*

	method of diagnosis: postoperative complaints by women Tubal patency method of diagnosis: by hysterosalpingogram after an interval of at least 3 menstrual cycles Pregnancy outcome method of diagnosis: occurrence and outcome of pregnancy, desire of pregnancy and follow-up not stated
Notes	Before medical therapy was installed, any free blood in the abdomen was suctioned off Women were discharged from the hospital when the urinary hCG level fell on 2 consecutive days

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Lundorff 1991a

Methods	Randomization during laparoscopy by sealed envelopes, with stratification into 6 subgroups based on age and an existing risk scoring scheme Single centre No power calculation Funding by Swedish Medical Research Council and by the Göteborg Medical Society Göteborg, Sweden Ethical committee approval Published as full paper
Participants	Hemodynamically stable women with a laparoscopically confirmed ampullary tubal pregnancy (< 4 cm) and a serum hCG concentration < 10,000 IU/l. Patients in whom the tubal pregnancy was not anatomically accessible for laparoscopic removal were excluded Number of women randomized 105 Number of women originally randomized 109, 4 secondary exclusions in the laparoscopy group for non tubal pregnancy and technical difficulties The trial was carried out at Sahlgrenska University Hospital, Göteburg, Sweden between May 1, 1987 and June 30, 1989
Interventions	Laparoscopy versus laparotomy
Outcomes	Treatment failure method of diagnosis: second operative intervention for persistent trophoblast and/or bleeding, or second line therapy with methotrexate for persistent trophoblast or abdominal pains or discomfort Operating time method of diagnosis: time from the start of uterine cannulation for diagnostic laparoscopy to application of bandage after surgery hCG resolution time method of diagnosis: number of days for serum hCG until nonpregnant levels (< 20 IU/l) Hospital stay method of diagnosis: number of days in the hospital

Lundorff 1991a *(Continued)*

	Total duration sick leave method of diagnosis: not stated, in days
Notes	Surgery was planned between 08.00 and 17.00 h Monday to Friday when at least two of five laparoscopic surgeons were on duty Risk scoring scheme: previous ectopic pregnancy, intra uterine device in situ, history of infertility, previous abdominal surgery, age < 27, 27-31, > 31 years All surgical procedures were planned as tube sparing linear salpingotomy regardless of the operative approach Note: In the study of Gray 1996, describing the economic analysis, numbers for primary treatment success were revised

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Lundorff 1991b

Methods	Randomization during laparoscopy by sealed envelopes, stratification into 6 subgroups based on age and an existing risk scoring scheme Single centre No power calculation Funding by Swedish Medical Research Council and by the Göteborg Medical Society Göteborg, Sweden Ethical committee approval Published as full paper
Participants	Hemodynamically stable women with a laparoscopically confirmed ampullary tubal pregnancy (< 4 cm) and a serum hCG concentration < 10,000 IU/l. Patients in whom the tubal pregnancy was not anatomically accessible for laparoscopic removal were excluded Number of women randomized: 73 Number of women originally randomized 109, 4 secondary exclusions, 18 no desire for pregnancy, 9 conceived before second look laparoscopy, 5 pregnancies by in vitro fertilization The trial was carried out at Sahlgrenska University Hospital, Göteburg, Sweden between May 1, 1987 and June 30, 1989
Interventions	Laparoscopy versus laparotomy
Outcomes	Pelvic adhesion formation method of diagnosis: adhesion and tubal score at second look laparoscopy in women with desire for future fertility after 1-29 weeks compared with the score at surgery of the tubal pregnancy by a risk scoring scheme. * Adhesion score (ipsi and contra lateral); impaired, unchanged and improved status * Tubal status (contra lateral); impaired, unchanged and improved status * Tubal patency (ipsi and contralateral); open or closed for dye solution at second look laparoscopy
Notes	Surgery was planned between 08.00 and 17.00 h Monday to Friday when at least two of five laparoscopic surgeons were on duty

Lundorff 1991b *(Continued)*

	Risk scoring scheme: previous ectopic pregnancy, intra uterine device in situ, history of infertility, previous abdominal surgery, age < 27, 27-31, > 31 years All surgical procedures were planned as tube sparing linear salpingotomy regardless of the operative approach Score system surface involved: (1/4, 2/4, 3/4, 4/4)location: ovary, proximal tube, distal tube adhesions: filmy, vascular, dense scoring: grade 1 absence, grade 2 mild, grade 3 moderate, grade 4 severe Scores were registered on a preprinted form and lysis of adhesions was noted Improvements of adhesions were regarded as unchanged status because improvement was considered a result of lysis of adhesions at primary surgery

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Lundorff 1992

Methods	Randomization by sealed envelopes, stratification into 6 subgroups based on age and an existing risk scoring scheme Single centre No power calculation Funding by Swedish Medical Research Council and by the Göteborg Medical Society Göteborg, Sweden Ethical committee approval Published as full paper
Participants	Hemodynamically stable women with a laparoscopically confirmed ampullary tubal pregnancy (< 4 cm) and a serum hCG concentration < 10,000 IU/l. Patients in whom the tubal pregnancy was not anatomically accessible for laparoscopic removal were excluded Number of women randomized: 87 Number of women originally randomized: 109, secondary exclusions 4, lost to follow up 1, no desire for pregnancy 17 The trial was carried out at Sahlgrenska University Hospital, Göteburg, Sweden between May 1, 1987 and June 30, 1989 with follow-up 1 year after surgery, or end of study period in August 1990
Interventions	Laparoscopy versus laparotomy
Outcomes	Fertility outcome method of diagnosis: cumulative frequency and pregnancy outcome of first subsequent pregnancy by means of questionnaires
Notes	Surgery was planned between 08.00 and 17.00 h Monday to Friday when at least two of five laparoscopic surgeons were on duty Risk scoring scheme: previous ectopic pregnancy, intra uterine device in situ, history of infertility, previous abdominal surgery, age < 27, 27-31, > 31 years All surgical procedures were planned as tube sparing linear salpingotomy regardless of the operative approach

Lundorff 1992 *(Continued)*

	A sub analysis was done to assess fertility outcome in patients with or without adhesions and in patients with or without bilateral patency, contralateral patency, and ipsilateral patency

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Mol 1999a

Methods	Randomization by a computer program with block randomization, with stratification for pre-existing tubal pathology and initial serum hCG concentration. Randomization was done before a confirmation laparoscopy Multi centre Tubal patency rate after laparoscopic salpingostomy was assumed to be 80%. A sample size of 100 women would allow to detect a difference in tubal patency rate, in favour of systemic methotrexate, of 18%, with a two-sided chi square test at p = 0.05 and with a power of 80% Funding by the Health Insurance Funds Council, Amstelveen, The Netherlands Ethical committee approval Intention to treat analysis Published as full paper
Participants	Hemodynamically stable women with a laparoscopically confirmed unruptured tubal pregnancy without fetal cardiac activity and no signs of active bleeding, no contraindications to receiving systemic MTX, (leucopenia, thrombocytopenia, or high concentrations of liver enzymes or serum creatinine) or contraindications to laparoscopic surgery, (documented extensive pelvic adhesions, large fibroid uterus, and severe ovarian hyperstimulation syndrome) Number of women randomised: 100 Number of women originally randomised 140 Secondary exclusions for non tubal pregnancy, tubal rupture, and/or active bleeding:40 The trial took place in six Dutch hospitals: the Academic Medical Centro of the University of Amsterdam, the Onze Lieve Vrouwe Gasthuis and the University Hospital Free University in Amsterdam and the University Hospitals of Groningen, Nijmegen and Utrecht, The Netherlands between January 1, 1994 and September 1, 1996
Interventions	Systemic MTX 1.0 mg/kg IM on days 0,2,4,6 alternated folinic acid 0.1 mg/kg oral on days 1,3,5,7 versus laparoscopic salpingostomy
Outcomes	Direct (medical) costs method of diagnosis: by multiplying used resources and resource unit prices. Used medical resources were duration of confirmation laparoscopy, duration of laparoscopic salpingostomy, conversions to salpingectomy, conversions to open surgery, initial injections with methotrexate, hospital stay from the moment of randomization in days, additional surgical and medical treatments, blood transfusions, consultations by other subspecialties, transvaginal sonograms, serum hCG measurements, and visits to the outpatient clinic. Resource unit prices reflected; unit costs for staff, materials, equipment, housing, depreciation, and overheads, the latter both at department level and at hospital level Indirect or time costs method of diagnosis: by multiplying used resources and resource unit prices. Used resources were professional and non-professional domiciliary care, transportation costs, and productivity loss. The price

Mol 1999a *(Continued)*

	of productivity loss was calculated with the friction method, based on age and sex stratified data of the Dutch population Mean costs method of diagnosis: sum of direct medical costs and indirect or time costs
Notes	Standardized unit costs were calculated for the Academic Medical Centre and subsequently applied to resource use observed in women treated in other centres over time Trial specific resource utilization and associated costs were excluded from the analysis Information concerning indirect (time) costs was collected by means of questionnaire. Of 30 women who did not complete the questionnaire, data was extrapolated The friction method presumes that in a situation of existing unemployment in society, workers are replaced 10 weeks after the onset of their disease by a previously unemployed worker. As a consequence, costs due to production loss are limited to a period of 10 weeks Correction for differential timing of economic costs was not appropriate Sensitivity analysis was performed to explore the effect of plausible changes in key variables on the results of the cost analysis. Key variables considered were; re intervention rate (surgical or medical), duration of initial hospital stay, number of transvaginal sonograms, number of serum hCG measurements, and duration of production loss Subgroup analysis was performed to evaluate if the costs of both treatments depended on patient characteristics at baseline. Patient characteristics considered in the subgroup analysis were presence of abdominal pain and the initial serum hCG concentration Scenario analysis was performed to estimate the costs of systemic methotrexate in a scenario without a confirmation laparoscopy and of systemic methotrexate in a single shot scenario

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Mottla 1992

Methods	Randomization before laparoscopy by using a random table Single centre No power calculation No source of funding stated Ethical committee approval Published as full paper
Participants	Hemodynamically stable women with a laparoscopically confirmed unruptured ectopic pregnancy (< 3 cm) and < 100 ml blood within the peritoneal cavity Number of women randomized: 12 Number of women ordinally randomized: 21, 9 secondary exclusions for non tubal pregnancy, non visibility of the pelvis, size of ectopic pregnancy > 3 cm

Mottla 1992 *(Continued)*

	The trial was carried out at Magee Womens hospital, USA between March 8, 1990 and November 13, 1990
Interventions	MTX 12.5 mg - 25 mg under laparoscopic control versus laparoscopic salpingostomy
Outcomes	Treatment success method of diagnosis:an uneventful decline of serum hCG to indictable levels (< 10 IU/l) Treatment failure method of diagnosis: surgical intervention for rising or plateau ing serum hCG concentrations Persistent trophoblast method of diagnosis: additional systemic MTX for persistent trophoblast, not defined Tubal patency method of diagnosis: by hysterosalpingogram, interval not stated Pregnancy outcome method of diagnosis: number of intrauterine pregnancies and repeat ectopic pregnancies
Notes	MTX 12.5 mg in 2 cc saline was changed after the first 3 patients to 25 mg in 7 cc saline In the MTX group 5 ml of normal saline containing 5 U of vasopressin was injected in the mesosalpinx and fallopian tube surrounding the hematosalpinx The study was discontinued because of poor results in the MTX injection group

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Nieuwkerk 1998a

Methods	Randomization by a computer program with block randomization, with stratification for pre-existing tubal pathology and initial serum hCG concentration. Randomization was done before a confirmation laparoscopy Multi centre Tubal patency rate after laparoscopic salpingostomy was assumed to be 80%. A sample size of 100 women would allow to detect a difference in tubal patency rate, in favour of systemic methotrexate, of 18%, with a two-sided chi square test at p = 0.05 and with a power of 80% Funding by the Health Insurance Funds Council, Amstelveen, The Netherlands Ethical committee approval Intention to treat analysis Published as full paper
Participants	Hemodynamically stable women with a laparoscopically confirmed unruptured tubal pregnancy without fetal cardiac activity and no signs of active bleeding, no contraindications to receiving systemic MTX, (leucopenia, thrombocytopenia, or high concentrations of liver enzymes or serum creatinine) or contraindications to laparoscopic surgery, (documented extensive pelvic adhesions, large fibroid uterus, and severe ovarian hyperstimulation syndrome) and with sufficient Dutch or English skills to complete questionnaires

Nieuwkerk 1998a *(Continued)*

	Number of women randomized: 79 Number of women originally randomized 140 Secondary exclusions for non tubal pregnancy, tubal rupture, and/or active bleeding: 40 Insufficient Dutch or English skills: 11 Lost to follow-up: 5 The trial took place in six Dutch hospitals: the Academic Medical Centre of the University of Amsterdam, the Onze Lieve Vrouwe Gasthuis and the University Hospital Free University in Amsterdam and the University Hospitals of Groningen, Nijmegen and Utrecht, The Netherlands between January 1, 1994 and September 1, 1996
Interventions	Systemic MTX 1.0 mg/kg IM on days 0,2,4,6 alternated folinic acid 0.1 mg/kg oral on days 1,3,5,7 versus laparoscopic salpingostomy
Outcomes	Health related quality of life method of diagnosis: health related quality of life over time (time effect), differences in health related quality of life between both treatment groups (treatment effect), and interaction between changes in health related quality of life over time and treatment group (time by treatment effect) was assessed by several standard self-administered psychometric measures with established reliability and validity The Medical Outcomes Study Short-form (MOS) comprises six sub-scales: physical functioning, role functioning and social functioning, mental health, health perceptions, and pain. A sub-scale measuring energy level was added to the original questionnaire The Rotterdam Symptom Checklist (RSCL) comprises four sub-scales: physical symptoms, psychological distress, activity level, and a single item measuring overall quality of life The State-Trait Anxiety Inventory (STAI) comprises specific measures of anxiety and depression The Self-rating Depression Scale (SDS) measures the subjective experience of depression as characterized by affective, cognitive, behavioural and psychological symptoms
Notes	The first set of questionnaires was completed after randomization but before confirmation laparoscopy. Patients received three sets of questionnaires when they were discharged from the hospital. These questionnaires were completed at home, two days, two weeks, and four weeks after confirmation laparoscopy. Women received the fifth set of questionnaires sixteen weeks after confirmation laparoscopy. Before and four weeks after confirmation laparoscopy only the MOS was administered. At other time points all questionnaires were administered. Trait anxiety was measured only once, two days after confirmation laparoscopy Reference values from the general population if available from manuals or the literature A sub analysis was performed taking into account the initial serum hCG concentration and the presence of abdominal pain at the start of treatment as covariate. A second sub analysis was performed, taking into account the presence of side effects of methotrexate after two weeks and the need for additional interventions after primary treatment as covariate, on data assessed at two weeks and four weeks after the start of treatment.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Rozenberg 2003

Methods	Randomization based on a computer generated list and balanced in blocks of variable size, stratified by centre, was carried out by sealed opaque envelopes, stored in the pharmacy of each hospital. The envelope was open end immediately before the allocated treatment was administered. Double blind, placebo controlled study, multi centre

Rozenberg 2003 *(Continued)*

	Success rate of methotrexate was assumed to be 80%. It was calculated that a sample size of 316 women had to be enrolled to demonstrate a benefit of > 15% in the methotrexate-miepristone group (i.e. success rate 95%) controlling for a type I error of 5% and a power of 90% (two-sided test) Funding by Assistance Publique- Hopiteaux de Paris, Delegation regionale a la Recherche Clinique Ethical committee approval Intention to treat analysis Published as full paper
Participants	Hemodynamically stable women > 18 years with no signs of active bleeding or haemoperitoneum in whom an ectopic pregnancy was diagnosed by using a non-laparoscopic algorithm combining transvaginal sonography (an unruptured mass, an ectopic pregnancy with fetal cardiac activity), quantitative serum hCG (serum hCG > 1,500 mIU/ml and no intra uterine sac seen by ultrasonography or serum hCG < 1,500 mIU/ml and a persistent abnormal increase [< 50% increase over 48 hr], and/or curettage showing no trophoblastic villi. Women must live within 1 hr drive from the hospital, should not be living alone, and have no contraindications for MTX or mifepristone (serum amino transferase concentrations > 2 fold the normal level, serum creatinine concentration > 1.5 mg/dl or leucopenia < 2,000/ml, thrombocytopenia < 100,000/ml, suprarenal gland dysfunction, active pulmonary disease, peptic ulcer disease, overt or biological evidence of immunodeficency, known sensitivity) Number of women randomized: 212 Lost to follow-up: 2 The trial took place between October 1999 and April 2001 in France in the following 18 centres: Dreux Hospital, Bichat-Claude Bernard Hospital Paris, La Conception Hospital Marseille, Clemenceau Hospital Caen, La Tronche Hospital Grenoble, Franco Britanic Hospital Levallois, Orsay Hospital, Boucicaut Hospital, Notre Dame de Bon-Secours Hospital Metz, Antoine Beclere Hospital Clamart, Poissy Saint Germain Hospital Poissy Cedex, CMCO Schiltigheim, CHRU Tours, Hotel Dieux Hospital Rennes, Jeanne de Flandre Hospital Lille, Evreux Hospital, Dreux Hospital, Paul gelle Hospital Roubaix, Annecy Hospital.
Interventions	Single dose systemic MTX (50 mg/m2 IM) alone versus the same regimen in combination with mifepristone 600 mg orally
Outcomes	Treatment success method of diagnosis: uneventful decline of serum hCG to undetectable levels (serum hCG < 10 mIU/ml) by primary treatment Persistent trophoblast method of diagnosis: if the serum hCG concentration on day 7 did not decrease by 15% as compared to the value on day 4 or fetal cardiac activity was still present on day 7 after the first or the subsequent dose of MTX. Persistent trophoblast was treated with single dose systemic MTX (50 mg/m2 im) Tubal preservation method of diagnosis: tubal preservation after primary treatment plus any additional conservative therapeutic interventions Side effects and complications method of diagnosis: follow-up of complete blood counts, liver and renal function tests, gastritis, stomatitis, abdominal pain, reversible alopecia hCG resolution time method of diagnosis: number of days for serum hCG to become undetectable Hospitalization time method of diagnosis: number of days in the hospital
Notes	A stopping rule was installed based on the triangular test (Whitehead 1992). This test consists of drawing stopping boundaries on the plot of the difference in efficacy against its precision, which complied with type I error and power requirements. If the computed points lay outside the boundaries, the trial was stopped. Inspections were done after inclusion of 60 women in each group.

Rozenberg 2003 *(Continued)*

	Two patients with persistent trophoblast refused a second injection of methotrexate and were treated surgically Two patients in the methotrexate alone group were lost to follow up One patient in the methotrexate-mifepristone group required emergency surgery for tubal rupture one day after serum hCG < 12 mIU/ml

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Sadan 2001

Methods	Double blind Method of randomization not stated Single centre No source of funding stated No power calculation Ethical committee approval not stated Published as full paper
Participants	Hemodynamically stable women with sonographically confirmed diagnosis of an extra uterine pregnancy with rising or plateau ing serum hCG levels who wished to preserve their fertility potential. At confirmation laparoscopy an intact tubal sac < 4 cm and no evidence of intra abdominal bleeding Number of women randomized: 20 The trial was carried out at Edith Wolson Medical Center, Holon, and Sackler Faculty of Medicine, Tel Aviv Israel. Timing and duration of the trial not stated
Interventions	MTX 25 mg in 3 ml fluid versus 3 ml hyperosmolar glucose 50% both into the gestational sac under laparoscopic guidance
Outcomes	Treatment success method of diagnosis: an uneventful decline of serum hCG to undetectable levels hCG resolution time method of diagnosis: mean daily decrease in serum hCG in % of the initial serum hCG Persistent trophoblast method of diagnosis: rising serum hCG levels for which an adjuvant intramuscular injection of MTX was given Hospitalization time method of diagnosis: number of days in the hospital
Notes	The study was discontinued after an interim analysis after 20 patients due to the higher failure rate in the hyperosmolar glucose group

Risk of bias

Bias	Authors' judgement	Support for judgement

Sadan 2001 *(Continued)*

Allocation concealment?	Unclear risk	B - Unclear

Saraj 1998

Methods	Randomization procedure by sealed envelopes Multi centre No power calculation No source of funding stated Ethical committee approval Published as full paper
Participants	Hemodynamically stable women in good maternal health weighing < 90 kg and desiring future pregnancy with an unruptured ectopic pregnancy < 3.5 cm on transvaginal sonography without fetal cardiac activity and no contraindications to receiving systemic MTX (hematocrit < 30%, white blood cell count < 2,000/mm3, platelet count < 100,000/mm3, elevated liver enzymes, medical disease (especially hepatic, renal or cardiac disease) and alcohol abuse Number of women initially randomized: 75 secondary exclusion for no ectopic pregnancy: 1 The trial was carried out at Women's and Children's Hospital of the Los Angeles County and University of Southern California Medical Centre, USA, between June 1995 and April 1997
Interventions	Single dose systemic MTX (1 mg/kg IM) versus laparoscopic salpingostomy
Outcomes	Treatment success method of diagnosis: complete elimination of the ectopic pregnancy (serum hCG < 15 IU/L) and preservation of the tube by primary treatment Persistent trophoblast method of diagnosis: in patients treated with systemic single dose MTX if the serum hCG concentration on day 7 did not decrease by 15% as compared to the value on day 4. In patients treated by salpingostomy, by postoperative rising or plateau ing serum hCG concentrations. In both treatment groups persistent trophoblast was treated with single dose systemic MTX (1 mg/kg IM). Tubal preservation method of diagnosis: tubal preservation after primary treatment plus any additional conservative therapeutic interventions hCG clearance time method of diagnosis: the median number of days to reach serum hCG concentrations < 15 IU/l Progesterone clearance time method of diagnosis: the median number of days to reach serum progesterone concentrations < 1.5 ng/ml Tubal patency method of diagnosis: by hysterosalpingography performed three months after completion of treatment Overall tubal patency method of diagnosis: tubal patency including those patients who underwent salpingectomy Fertility outcome method of diagnosis: pregnancy outcome of first subsequent pregnancy nine months after treatment

Saraj 1998 *(Continued)*

Notes	The diagnosis ectopic pregnancy was based on history, physical examination, transvaginal sonography and quantitative serum hCG concentrations using a diagnostic algorithm including uterine curettage In the MTX group women were treated on an outpatient basis. In the laparoscopy group women were hospitalized for 6-8 hours postoperatively.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Sharma 2003

Methods	Randomization procedure by computer generated numbers Single centre No power calculation No source of funding stated Ethical committee approval Published as full paper
Participants	Patients with suspected ectopic pregnancy and no significant medical disease like diabetes, hypertension or previous laparotomy Number of women randomized: 60 The trial was carried out at Maulana Azad Medical College and associated Lok Nayak Hospital, New Delhi-110002, India between January 1998 to March 2001
Interventions	Minilaparotomy versus laparotomy
Outcomes	Mean operative time method of diagnosis: in minutes Per and postoperative complications: method of diagnosis: mean blood loss in ml, number of patients with blood transfusions, fever, paralytic ileus, urinary tract infections and wound infection Mobility method of diagnosis: mean day of mobility, starting normal diet, discharge from hospital
Notes	The minilaparotomy technique is an incision of the skin by 4-6 cm long suprapubic transverse incision and opening of the abdomen by Cohen's technique (tearing rectus sheath laterally and peritoneum with fingers). The fundus of the uterus was exteriorised along with the affected tube using 2 fingers. No packs or retractors were used. Antibiotics were 3 doses of 1.2 g Coamoyclav at 8 hourly intervals. The choice of type and length of the incision in the (standard) laparotomy group (more than 6 cm incision) was left to the operating surgeon. Antibiotics were ciprofloxacin and metronidazole for 7 days Laparoscopy was performed to confirm the diagnosis ectopic pregnancy in 19 out of 30 in the minilaparotomy group (63%) and 15 out of 30 (50%) in the laparotomy group

Sharma 2003 *(Continued)*

	Salpingostomy or salpingectomy was performed depending on the age, parity and condition of the affected and opposite tube

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Shulman 1992

Methods	Method of randomization not stated Single centre No power calculation No source of funding stated Ethical committee approval not stated Published as full paper
Participants	Hemodynamically stable women with a laparoscopically confirmed unruptured tubal pregnancy (< 4 cm) without active bleeding Number of women randomized: 15 The trial was carried out at Sapir Medical Centre, Kfar Saba Israel during an 18 month period
Interventions	MTX 12.5 mg in 7 ml under laparoscopic guidance versus MTX 12.5 mg in 7 ml physiologic solution under laparoscopic guidance combined with systemic MTX 0.5 mg/kg orally (days 0,2,4,6,8) alternated with folinic acid 0.1 mg/kg (days 1,3,5,7,9)
Outcomes	Treatment success method of diagnosis: uneventful decline of serum hCG to undetectable levels Treatment failure method of diagnosis: tubal rupture hCG resolution time method of diagnosis: number of days for serum hCG to become undetectable Corpus luteum activity method of diagnosis: serum hCG 17ßE2 and progesterone clearance rate Intraoperative complications and side effects method of diagnosis: postoperative complaints, blood cell count, liver enzymes and kidney function
Notes	At laparoscopy any free blood was suctioned away

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Sowter 2001a

Methods	Unblocked randomization procedure by a computer programme and allocation details were contained in sequentially numbered opaque envelopes sealed by a third party Open pragmatic multi centre randomized controlled trial Power calculations were made for detecting differences in treatment success rate using a two sided (2 test at a 5% level of significance and with a study power of 80%. It was assumed in these calculations that in women with a serum hCG level under 5000 IU/l a persistent trophoblast rate of 5% or less following laparoscopic surgery could be expected. To detect a difference in treatment success rate of 20%, 49 women in each group would be needed No source of funding stated Ethical committee approval Intention to treat analysis Published as full paper
Participants	Hemodynamically stable women with an unruptured tubal pregnancy < 3.5 cm and minimal haemoperitoneum on transvaginal sonography (<300 mL) without fetal cardiac activity and a rising serum hCG < 5,000 IU/l and no contraindications to MTX (leukopenia, thrombocytopaenia, elevated serum liver enzymes or creatinine) or contraindications to laparoscopic surgery, (documented extensive pelvic adhesions, large fibroid uterus, and severe ovarian hyperstimulation syndrome) Number of women initially randomized: 62 lost to follow-up: 7 The trial was carried out at three hospitals in Auckland, New Sealand, (National Women's Hospital, North Shore Hospital, Middlemore Hospital) between 28 July 1997 and 27 September 1998
Interventions	Multiple dose systemic MTX (50 mg/m2) versus laparoscopic surgery (single dose data available)
Outcomes	Treatment success method of diagnosis: complete elimination of the ectopic pregnancy (serum hCG < 5 IU/L) and preservation of the tube by primary treatment Persistent trophoblast method of diagnosis: in patients treated with systemic single dose MTX if the serum hCG concentration between day 4 and day 7 did not decrease by 15% as compared to the value on day 0, or was plateau ing or rising after day 7. In patients treated by salpingostomy, if the serum hCG concentration on day 7 did not decrease by 50% as compared to the value on day 0, or was plateau ing or rising after day 7. In both treatment groups persistent trophoblast was treated with single dose systemic MTX Tubal preservation method of diagnosis: tubal preservation after primary treatment plus any additional conservative therapeutic interventions hCG clearance time method of diagnosis: the median number of days to reach serum hCG concentrations < 5 IU/l Tubal patency method of diagnosis: by hysterosalpingography performed three months after completion of follow-up Overall tubal patency method of diagnosis: tubal patency including those patients who underwent salpingectomy Health related quality of life method of diagnosis: differences in health related quality of life between both treatment groups was assessed by several psychological and side effects questionnaires at the time of trial entry, day 4,10 and 28

Sowter 2001a *(Continued)*

	The Short-form 36 (SF-36) comprises eight sub-scales: physical functioning, physical role limitation, bodily pain, social role limitation, general mental health, role limitation due to emotional problems, vitality, and general health perception. The state scale of the State-trait anxiety Inventory 21: A 20-item state scale measuring current anxiety. The Centre for Epidemiologic Studies Depression (CES-D) scale 22: A 20-item depression scale designed to identify depression in the general population. The physical symptom component of the Rotterdam symptom checklist 23: A four component (physical symptoms, psychological distress, activity level, and quality of life) questionnaire originally used to assess the health related quality of life of patients receiving cancer treatment. The questionnaire was modified by the addition of possible side effects relevant to the treatment of ectopic pregnancy (shoulder-tip pain, pelvic pain, vaginal bleeding) and by asking women to also record the number of days on which side effects were experienced and any additional symptoms they considered to be possible side-effects
Notes	A non laparoscopic diagnostic algorithm was used to diagnose the presence of an ectopic pregnancy The authors stated that salpingotomy was always performed in preference of salpingectomy. In this review the results of the medical outcome measures were recalculated as if the comparison were single dose systemic MTX (50 mg/m2) versus laparoscopic salpingotomy

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Sowter 2001b

Methods	Unblocked randomization procedure by a computer programme and allocation details were contained in sequentially numbered opaque envelopes sealed by a third party Open pragmatic multi centre randomized controlled trial Power calculations were made for detecting differences in treatment success rate using a two sided (2 test at a 5% level of significance and with a study power of 80%. It was assumed in these calculations that in women with a serum hCG level under 5000 IU/l a persistent trophoblast rate of 5% or less following laparoscopic surgery could be expected. To detect a difference in treatment success rate of 20%, 49 women in each group would be needed No source of funding stated Ethical committee approval Intention to treat analysis Published as full paper
Participants	Hemodynamically stable women with an unruptured tubal pregnancy < 3.5 cm and minimal haemoperitoneum on transvaginal sonography (300mL) without fetal cardiac activity and a rising serum hCG < 5,000 IU/l and no contraindications to MTX (leukopenia, thrombocytopaenia, elevated serum liver enzymes or creatinine) or contraindications to laparoscopic surgery, (documented extensive pelvic adhesions, large fibroid uterus, and severe ovarian hyperstimulation syndrome) Number of women initially randomized: 62 The trial was carried out at three hospitals in Auckland, New Sealand, (National Women's Hospital, North Shore Hospital, Middlemore Hospital) between 28 July 1997 and 27 September 1998
Interventions	Single dose systemic MTX (50 mg/m2) versus laparoscopic surgery

Sowter 2001b *(Continued)*

Outcomes	Direct costs method of diagnosis: by multiplying used resources and resource unit prices, i.e.. costs of investigations, initial and follow-up visits to the gynecology assessment unit, drugs used, operative and anaesthetics, in patients hotel, and any costs associated with additional treatments, hospital readmission and complications Indirect costs method of diagnosis: the reduction of paid and unpaid production due to patient's treatment and costs of transport and other (non) medical expenses
Notes	Standardized unit costs were calculated for the National Women's Hospital and subsequently applied to resource use observed in women treated in other two centres Trial specific resource utilization and associated costs were excluded from the analysis Information concerning indirect costs was collected by means of questionnaire. Of 4 women who did not complete the questionnaire, data was extrapolated Sensitivity analysis was performed on direct costs for each cost component assuming that unit costs were 50%, 150% and 200% of base case unit costs Subgroup analysis was performed to explore the effect of serum hCG on the results of the cost analysis Scenario analysis was performed to determine the overall costs savings per patient if all eligible women were treated with MTX

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Tulandi 1991a

Methods	Method of randomization not stated Single centre No power calculation No source of funding stated Ethical committee approval Published as full paper
Participants	Women with an unruptured ampullary ectopic pregnancy at laparotomy with the contralateral tube in situ and no history of a recurrent ectopic pregnancy Number of women randomized: 34 number of women for second look laparoscopy: 18 The trial was carried out at Royal Victoria Hospital Mc Gill University Montral, Quebec, Canada Time and duration of the trial not stated
Interventions	Salpingostomy without tubal suturing versus salpingostomy with tubal suturing
Outcomes	Treatment success method of diagnosis: an uneventful postoperative course

Tulandi 1991a *(Continued)*

	Periadnexal adhesions method of diagnosis: degree of adhesions conform the American Fertility Society classification at second look laparoscopy/laparotomy for recurrent ectopic pregnancy, follow-up not stated Tubal fistula Method of diagnosis: at second look laparoscopy Reproductive performance method of diagnosis: cumulative intrauterine and ectopic pregnancy probability at 12 and 24 months, desire of pregnancy not stated
Notes	Surgery was performed by laparotomy Desire of pregnancy is not stated Intra uterine pregnancy is not divided into viable pregnancies or abortions

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Tzafettas 1994

Methods	Method of randomization not stated Multicenter No power calculation No source of funding stated Ethical committee approval not stated Published as full paper
Participants	Hemodynamically stable women with an unruptured ectopic pregnancy (< 4cm) confirmed by ultrasound (identification of the gestational sac) or when not visible by laparoscopy, serum hCG not declining in two consecutive measurements at least 24 hrs apart, and < 100 ml of blood in the pelvis Number of women randomized: 36 The trial was carried out at University Department of Obstetrics and Gynecology in the Hippokrateio Hospital and the Blue Cross Infertility Centre Thessaloniki, Greece between November 1992 and November 1993
Interventions	MTX 100 mg in 4 ml saline transvaginally under sonographic guidance versus MTX 100 mg in 4 ml saline under laparoscopic guidance
Outcomes	Treatment success method of diagnosis: an uneventful decline of serum hCG to undetectable levels (< 20 IU/l) Treatment failure method of diagnosis: laparotomy for detection of nearly 100 ml blood in the pouch of Douglas at transvaginal sonography or persistent lower abdominal pain Persistent trophoblast method of diagnosis: additional 50 mg MTX in 2 ml saline was installed into the affected fallopian tube by trans uterine tubal catheterisation for no decline in serum hCG within 10 days

Tzafettas 1994 *(Continued)*

	hCG resolution time method of diagnosis: number of weeks for serum hCG to become < 20 IU/l Serum MTX levels method of diagnosis: venous blood sample twice weekly determination by fluorescence polarization immunoassay Side effects method of diagnosis: not stated
Notes	Before injecting medical therapy the tubal content was aspirated

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Ugur 1996

Methods	Method of randomization not stated, with stratification for size of the ectopic pregnancy Single centre No power calculation No source of funding stated Ethical committee approval not stated Published as full paper
Participants	Hemodynamically stable women with a laparoscopically confirmed unruptured ectopic pregnancy (< 5 cm) Number of women randomized: 40 The trial took place in the Reproductive Endocrinology and Endoscopic Surgery Clinic of Tahir Burak Women's Hospital, Ankara, Turkey between January 1993 and December 1994
Interventions	Laparoscopic salpingotomy with prophylactic vasopressin injection 5-10 ml (5IU diluted in 20 ml saline) into the proximal and distal mesosalpinx versus laparoscopic salpingotomy alone
Outcomes	Electrocoagulation for hemostasis method of diagnosis: number of women requiring electrocoagulation for hemostasis Treatment failure method of diagnosis: number of women requiring a conversion to laparotomy for failed hemostasis at laparoscopy Persistent trophoblast method of diagnosis: not defined Operation time method of diagnosis: operation time in minutes hCG clearance time method of diagnosis: rate and magnitude to reach undetectable serum hCG levels (< 10 IU/l) Complications

Ugur 1996 *(Continued)*

	method of diagnosis: potential complications of vasopressin (hypertension, bradycardia, delayed bleeding) % change of hemoglobin postoperatively Tubal patency method of diagnosis: by hysterosalpingogram 3 months after the operation in women successfully treated by primary treatment
Notes	In women with persistent bleeding from the tube after removal of the trophoblastic tissue, bleeding points were identified and controlled with bipolar coagulation, with an effort not to damage the tubal mucosa. If bleeders were not precisely localized, pressure was applied to stop the bleeding. If still unsuccessful, hemostasis was attempted in the mesosalpingeal arcade when possible. To avoid a salpingectomy and any further damage to the tube by extensive electrocoagulation, hemostasis was attempted at length by laparotomy

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Vermesh 1989

Methods	Randomization at the time of laparoscopy by sequential selection of unmarked opaque envelopes containing a coded card Single centre No power calculation Funding by National Institute of Health Ethical committee approval Published as full paper
Participants	Hemodynamically stable women with a laparoscopically confirmed unruptured isthmic or ampullary tubal pregnancy (< 5 cm) without pelvic adhesions precluding complete visualisation of the pelvis Number of women randomized: 60 The trial was carried out at Women's Hospital, University of Southern California, Los Angeles USA between October 1986 and February 1988
Interventions	Salpingostomy by laparoscopy versus salpingostomy by laparotomy
Outcomes	Morbidity method of diagnosis: intraoperative estimated blood loss, intraoperative complications, short term complications, persistent trophoblast, long term complications Persistent trophoblast method of diagnosis: second operation for persistently rising serum hCG titers hCG resolution time method of diagnosis: number of days for serum hCG to become undetectable (< 1.5 IU/l) Hospital stay method of diagnosis: not stated, in days Return to full activity method of diagnosis: not stated, in days

Vermesh 1989 *(Continued)*

	Costs method of diagnosis: not stated, related with hospital stay Tubal patency method of diagnosis: by hysterosalpingogram 12 weeks after treatment Fertility outcome method of diagnosis: pregnancy rates and pregnancy outcome in patients trying to conceive, contacted by telephone follow-up 6 months
Notes	During operation other pelvic fertility factors were assessed, and the maximal amount of surgery directed toward the contralateral tube was lysis of adhesions

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Vermesh 1992

Methods	Randomization by sequential selection of unmarked opaque envelopes containing a coded card Single centre No power calculation No source of funding stated Ethical committee approval Published as full paper
Participants	Hemodynamically stable women with a laparoscopically confirmed unruptured isthmic or ampullary tubal pregnancy (< 5 cm) without pelvic adhesions precluding complete visualisation of the pelvis Number of women randomized: 40 Number of women originally randomized 60, 15 lost to follow up, 5 no desire future pregnancy The trial was carried out at Women's Hospital, University of Southern California, Los Angeles USA between October 1986 and February 1988
Interventions	Salpingostomy by laparoscopy versus salpingostomy by laparotomy
Outcomes	Reproductive outcome after 1 and 3 years method of diagnosis: pregnancy outcome and life table analysis by means of periodic office visits, telephone calls, and letters, medical records, or records maintained by the Public Health Department
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Wang 1998

Methods	Method of randomization not stated Randomization in a 1:2 scheme Single centre No power calculation No source of funding stated Ethical committee approval not stated Published as full paper
Participants	Women with a swollen fallopian tube at gynecological examination, ectopic pregnancy seen with ultrasound and serum hCG > 3.1 microg/L Number of women randomised: 78 The trial was carried out at Health of Mothers and Children Hospital in Shanxi province, China during a three months period
Interventions	Single dose systemic MTX 50-70 mg/m2 IM versus the same regimen in combination Ectopic Pregnancy 2 (EP2) decoction, ie a chinese herb one dose a day, one dose per two days in the last two months
Outcomes	Treatment success method of diagnosis: an uneventful decline of serum hCG to un decidable levels Fertility outcome method of diagnosis: pregnancy outcome serum hCG clearance time method of diagnosis: number of days for serum hCG to become undetectable Ectopic pregnancy disappearance time method of diagnosis: mean number of days for the ectopic mass to become undetectable
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Yalcinkaya 1996

Methods	Method of randomization not stated Double blind study, single center No power calculation No source of funding stated Ethical committee approval not stated Published as abstract

Yalcinkaya 1996 *(Continued)*

Participants	Hemodynamically stable women with an ectopic pregnancy < 3.5 cm on transvaginal sonography with rising or plateau ing serum hCG concentrations without liver or kidney disease Number of women initially randomized: 41 Lost to follow-up: 1 The trial was carried out at West Verginia University Health Sciences Center, Charleston Division, Charleston, West Verginia, USA between January 1994 and March 1996
Interventions	Single dose systemic MTX 25 mg/m2 IM versus single dose systemic MTX 50 mg/m2 IM
Outcomes	Treatment success method of diagnosis: complete elimination of the ectopic pregnancy (serum hCG < 5 IU/L) and preservation of the tube by primary treatment Persistent trophoblast method of diagnosis: if the serum hCG concentration on day 7 did not decrease by 15% as compared to the value on day 4. Persistent trophoblast was treated with single dose systemic MTX. Treatment failure method of diagnosis:tubal rupture or significant haemoperitoneum presenting with severe abdominal pain and falling haemoglobin hCG clearance time method of diagnosis: the median number of days to reach serum hCG concentrations < 5 IU/l Side effects method of diagnosis: MTX related side effects were recorded and complete blood count and AST levels
Notes	Ectopic pregnancy was diagnosed by history and examination

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Yalcinkaya 2000

Methods	Randomization by sealed envelopes at the central pharmacy Double blind block randomized study, single center The need for a second MTX injection with MTX 50 mg was 28%. It was calculated in this bio equivalency study that 47 women were needed to detect an increase to 56% with a power of 0.80. No source of funding stated Ethical committee approval not stated Published as abstract
Participants	Hemodynamically stable women with an ectopic pregnancy < 3.5 cm on transvaginal sonography with rising or plateau ing serum hCG concentrations without liver or kidney disease and desire for future pregnancy Number of women randomized: 100 Number of patients available for fertility follow-up: 56

Yalcinkaya 2000 *(Continued)*

	The trial was carried out at West Verginia University Health Sciences Centre, Charleston Division, Charleston, West Verginia, USA between January 1994 through September 1998
Interventions	Single dose systemic MTX 25 mg/m2 IM versus single dose systemic MTX 50 mg/m2 IM
Outcomes	Treatment success method of diagnosis: complete elimination of the ectopic pregnancy (serum hCG < 5 IU/L) and preservation of the tube by primary treatment Persistent trophoblast method of diagnosis: if the serum hCG concentration on day 7 did not decrease > 15% as compared to the value on day 4. Persistent trophoblast was treated with single dose systemic MTX. Treatment failure method of diagnosis: tubal rupture or significant haemoperitoneum presenting with severe abdominal pain and falling haemoglobin hCG clearance time method of diagnosis: the median number of days to reach serum hCG concentrations < 5 IU/l Side effects method of diagnosis: MTX related side effects were recorded and complete blood count and AST levels Tubal patency method of diagnosis: by hysterosalpingography
Notes	MTX injection could only be repeated once

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Zilber 1996

Methods	Method of randomization not stated Single centre No power calculation No source of funding stated Ethical committee approval not stated Published as full paper
Participants	Women with a laparoscopically confirmed unruptured tubal pregnancy tubal pregnancy (< 3 cm) without active bleeding and full visualization of the pelvis Number of women randomized: 48 The trial was carried out at Assaf Harofeh Medical Center, Israel between January 1991 and December 1992
Interventions	MTX 25 mg in 3 ml physiologic solution under laparoscopic guidance versus laparoscopic salpingostomy
Outcomes	Treatment success

Zilber 1996 *(Continued)*

	method of diagnosis: an uneventful decline of serum hCG (< 10 IU/l) Treatment failure method of diagnosis: additional single systemic injection of MTX or surgical intervention for persistent trophoblast Persistent trophoblast method of diagnosis: persistently rising serum hCG concentrations hCG resolution time method of diagnosis: number of days for serum hCG to become < 10 IU/L Intra-operative blood loss method of diagnosis: amount of blood loss in millilitres Operation time method of diagnosis: duration of operation in minutes Hospitalization time method of diagnosis: number of days in the hospital Complications method of diagnosis: wound infection, fever, blood transfusions Pregnancy outcome method of diagnosis: number of intrauterine pregnancies in patients with further attempts at conceiving was assessed by telephone calls and letters
Notes	Follow-up up to 18 months: 34 with desire for future fertility

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

hCG: human chorionic gondaotrophin, IM: intra muscular, IVF: invirto fertilization, WBC: white blood cell, MTX: methotrexate, PGF: prostaglandin

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Colacurci 1998	This multicenter study compared single dose systemic MTX (50 mg IM) versus laparoscopic salpingostomy in 33 hemodynamically stable women with an unruptured ectopic pregnancy < 4 cm on transvaginal sonography with serum hCG concentrations < 10,000 IU/l and no hepatic or renal dysfunction or abnormal blood count. The trial was carried out at Second University of Naples and Federico II University, Naples, Italy, between January 1994 and March 1995. The method of randomization was by hospital number, reason for exclusion.
Kaya 2002	This study compared laparoscopic salpingotomy and a single dose of intratubal MTX preoperatively (1 mg/kg) versus salpingotomy alone in 65 hemodynamically stable women with a tubal pregnancy (< 4 cm) without evidence of tubal rupture and no signs of hepatic or kidney disfunction who underwent salpingotomy. The trial was carried out in University of Suleyman Demiral Isparta 32040 in Turkey. Timing and duration of the trial not stated.

Study	Reason for exclusion
	Method of randomization was by hospital number in a 1:2 scheme, reason for exclusion.
Koninckx 1991	This study compared laparoscopic salpingostomy by CO2 laser versus microsurgical salpingotomy by laparotomy in hemodynamically stable women with an ectopic pregnancy. The trial was carried out at University Hospital Gasthuisberg, Leuven, Belgium between 1988 and 1 December 1989 and was funded by NFWO (Belgian National Foundations for Research). This study is not seen as a randomised controlled trial nor a controlled clinical trial whereas treatment was dependent on the surgeon in charge. Only two surgeons were capable of doing laser-endoscopy whereas the other consultants only performed microsurgery.
Laatikainen 1993	This study compared hyperosmolar glucose (50%) in 10-20 ml under laparoscopic guidance versus laparoscopic salpingostomy in 40 women with a laparoscopically confirmed unruptured tubal pregnancy (< 4 cm) without fetal cardiac activity, and a serum hCG concentration < 5000 IU/l and no history of a recurrent ectopic pregnancy. The trial was carried out at Oulo University Central Hospital, Oulu, Finland between October 1990 and February 1992. Randomization by even or odd day of birth, reason for exclusion.
Lund 1955	This study has been frequently quoted as being the first randomised controlled trial in the treatment of ectopic pregnancy. However, if carefully read, this study really is a retrospective comparative study comparing expectant management versus open surgery in women with ectopic pregnancy. Lund described in 1955 the short and long term outcome of two standard treatment regimens in 204 women, who had been treated for ectopic pregnancy between 1930 and 1946 at the Gentofte County hospital in Copenhagen, Denmark. In two departments of this hospital standard treatment for "subacute women with a typical course of ectopic pregnancy and a positive pregnancy test, who had no demonstrable hemoperitoneum on admission and were not acutely ill" was confinement to bed until the pregnancy test became negative and pain ceased (n=119), whereas in one other department all such women were consistently subjected to operation (n=85). Expectant management was successful in 57% (68/119) of women. In 20% (27/119) an operation was done for signs of a large intra abdominal haemorrhage, ie. "catastrophe" , whereas in 23% (24/119) of women an operation was done after 4 weeks stay in the hospital with no signs of the disease becoming quiescent. Fertility outcome in patients with desire for future pregnancy was similar in the expectant management group (n=101) and in the surgery group (n=73). The intra uterine pregnancy rate was 46% and 44%, respectively whereas the repeat ectopic pregnancy rate was 15% in both treatment groups. Reasons for exclusion: 1. This study is not a randomized controlled trial. 2. The diagnosis ectopic pregnancy does not meet the inclusion criteria as defined for this review, i.e.. by the transvaginal sonographic finding of an ectopic gestational sac with an empty uterus, by a serum hCG discriminatory zone principle with an empty uterus, and/or by laparoscopy or by open surgery.
Murphy 1992	This study compared laparoscopy versus laparotomy in 63 hemodynamically stable women with a laparoscopically confirmed ectopic pregnancy. Number of women originally randomized 73. Secondary exclusions in the laparoscopy group: non tubal pregnancy (1), unavailability of equipment (3), unavailability of trained physicians (3), dense adhesions (1), uncontrollable bleeding from the mesosalpinx (1), excessive size of the ectopic pregnancy (1). The trial was carried out at University of California, San Diego Medical Centre, California, USA between April 1988 and December 1989. Method of randomization was on alternating months, reason for exclusion.

Study	Reason for exclusion
O'Shea 1994	This study compared MTX 20 mg in 0.8 ml normal saline under laparoscopic guidance versus laparoscopic salpingostomy by CO2 laser in 53 hemodynamically stable women with a laparoscopically confirmed unruptured ectopic pregnancy (< 4 cm). The trial was carried out at Flinders University and Flinders Medical Centre, Adelaide Australia. Method of randomization was before laparoscopy on the basis of hospital numbers, reason for exclusion.
Porpora 1996	This study compared MTX 20 - 50 mg in 4 ml saline solution under laparoscopic guidance and oral calcium folinate 16.2 mg/day (day 1-7) versus laparoscopic salpingostomy in 14 hemodynamically stable women a laparoscopically confirmed unruptured tubal ampullary pregnancy (< 5 cm) without fetal cardiac activity. The trial was carried out at La Sapienza, University of Rome, Rome Italy between July 1991 to May 1994. Method of randomization was that the first seven consecutive women meeting the inclusion criteria were treated medically, whereas the following seven women by laparoscopic salpingostomy. This was the reason for exclusion.

MTX: methotrexate, CO2 : carbon dioxide, IM: intramuscular, hCG : human chorionic gonadotrophin.

Characteristics of ongoing studies *[ordered by study ID]*

Fernandez 1

Trial name or title	Randomized controlled trial between medical treatment by methotrexate versus conservative surgical treatment to evaluate subsequent fertility
Methods	
Participants	Patients > 18 years diagnosed with a non active ectopic pregnancy defined by score or algorithm and with desire of future pregnancy Exclusion criteria: pregnant after failed contraception or after IVF-ET
Interventions	Single dose methotrexate versus laparoscopic conservative surgery with a single dose methotrexate postoperatively
Outcomes	Primary outcome is subsequent fertility with 2 years follow up. Secondary outcomes are complications of treatment; time to hospitalisation; serum hCG clearance curve; success rate
Starting date	08-2004
Contact information	Fernandez H, Antoine Beclere Hospital Clamart, France
Notes	Multicenter study in France

Fernandez 2

Trial name or title	Randomised controlled trial between conservative versus radical surgical treatment to evaluate subsequent fertility
Methods	
Participants	Patients > 18 years diagnosed with ectopic pregnancy by ultrasound and with desire of future pregnancy Exclusion criteria: pregnant after failed contraception or after IVF-ET
Interventions	Conservative versus radical surgery both laparoscopically
Outcomes	Primary outcome is subsequent fertility with 2 years follow up every 6 months. Secondary outcomes are complications of treatment; time to hospitalisation; serum hCG clearance curve; success rate
Starting date	08-2004
Contact information	Fernandez H, Antoine Beclere Hospital Clamart, France
Notes	Multicenter study in France

Hajenius 1

Trial name or title	A randomised controlled trial of salpingostomy versus salpingectomy for tubal pregnancy; impact on future fertility
Methods	
Participants	All hemodynamically stable women > 18 years with a presumptive diagnosis of tubal pregnancy, who are scheduled for surgical treatment Exclusion criteria: no desire for future pregnancy, pregnant after IVF-ET, tubal rupture whenever this tubal rupture interferes with the possibility to perform a salpingostomy, contralateral tubal pathology
Interventions	salpingostomy versus salpingectomy (by laparoscopy or by laparotomy)
Outcomes	Primary outcome measure is the occurrence of a spontaneous vital intra uterine pregnancy. Other outcome measures are repeat ectopic pregnancy, costs (including duration of surgery, additional costs of persistent trophoblast or repeat ectopic pregnancy, or other peri/per/post operative complications and start of fertility treatment, ie. IVF-ET), patients' preferences.
Starting date	01-09-2004
Contact information	Hajenius PJ. Academic Medical Center, University of Amsterdam, The Netherlands
Notes	International multicenter trial in the Netherlands, Sweden, Norway, Denmark, United Kingdom

Hajenius 2

Trial name or title	Randomised controlled trial of systemic MTX in an intramuscular single shot regimen versus expectant management
Methods	
Participants	Inclusion criteria: Hemodynamically stable women > 18 years with suspected ectopic pregnancy in whom serum hCG concentration is < 2,000 IU/L but plateauing at three measurements with 2-days intervals. Exclusion criteria: viable ectopic pregnancy, abnormalities in liver or renal function or in full blood count
Interventions	systemic MTX (1 mg/kg) in an intramuscular single shot regimen versus expectant management
Outcomes	Primary outcome is an uneventful decline of serum hCG to an undetectable level by primary treatment. Secondary outcomes are number of (re)interventions (additional MTX or surgical procedures), treatment complications, future fertility, health related quality of life, financial costs, and patients' preferences
Starting date	01-02-2006
Contact information	Hajenius PJ. Academic Medical Center, University of Amsterdam, The Netherlands
Notes	Multicenter study in the Netherlands

Jurkovic

Trial name or title	Randomised double blind placebo controlled trial of single dose methotrexate versus expectant management in women with tubal ectopic pregnancy
Methods	
Participants	Inclusion criteria: Hemodynamic stability No hemoperitoneum Non-viable pregnancy hCG < 1,500 IU/l Normal renal, liver function and normal blood parameters
Interventions	systemic MTX 50 mg/m2 im versus saline as placebo
Outcomes	The primary outcome measure is the number of surgical procedures. The secondary outcome measure is the intra uterine pregnancy rate within 3 years.
Starting date	01-09-2005
Contact information	Jurkovic D. Early Pregnancy Unit, Kings Hospital, London, United Kingdom
Notes	Single center study

DATA AND ANALYSES

Comparison 1. laparoscopic salpingostomy versus salpingostomy by open surgery

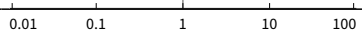
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 primary treatment success	2	165	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.28 [0.09, 0.86]
2 persistent trophoblast	2	165	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.47 [1.06, 11.28]
3 tubal patency	2	110	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.58 [0.23, 1.42]
4 subsequent intrauterine pregnancy	2	127	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.21 [0.59, 2.45]
5 repeat ectopic pregnancy	2	127	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.47 [0.15, 1.47]

Analysis 1.1. Comparison 1 laparoscopic salpingostomy versus salpingostomy by open surgery, Outcome 1 primary treatment success.

Study or subgroup	laparoscopy n/N	open surgery n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Lundorff 1991a	42/48	55/57		61.38%	0.28[0.07,1.19]
Vermesh 1989	26/30	29/30		38.62%	0.28[0.04,1.7]
Total (95% CI)	**78**	**87**		**100%**	**0.28[0.09,0.86]**
Total events: 68 (laparoscopy), 84 (open surgery)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.99); I^2=0%					
Test for overall effect: Z=2.21(P=0.03)					

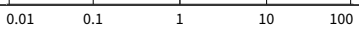
Analysis 1.2. Comparison 1 laparoscopic salpingostomy versus salpingostomy by open surgery, Outcome 2 persistent trophoblast.

Study or subgroup	laparoscopy n/N	open surgery n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Lundorff 1991a	8/48	2/57		82.18%	4.54[1.23,16.68]
Vermesh 1989	1/30	1/30		17.82%	1[0.06,16.37]
Total (95% CI)	**78**	**87**		**100%**	**3.47[1.06,11.28]**
Total events: 9 (laparoscopy), 3 (open surgery)					
Heterogeneity: Tau^2=0; Chi^2=0.92, df=1(P=0.34); I^2=0%					
Test for overall effect: Z=2.06(P=0.04)					



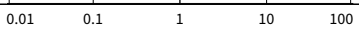
Analysis 1.3. Comparison 1 laparoscopic salpingostomy versus salpingostomy by open surgery, Outcome 3 tubal patency.

Study or subgroup	laparoscopy n/N	open surgeryl n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Lundorff 1991b	22/29	31/38		58.54%	0.71[0.22,2.31]
Vermesh 1989	16/23	17/20		41.46%	0.43[0.11,1.75]
Total (95% CI)	**52**	**58**		**100%**	**0.58[0.23,1.42]**
Total events: 38 (laparoscopy), 48 (open surgeryl)					
Heterogeneity: Tau^2=0; Chi^2=0.29, df=1(P=0.59); I^2=0%					
Test for overall effect: Z=1.19(P=0.23)					



Analysis 1.4. Comparison 1 laparoscopic salpingostomy versus salpingostomy by open surgery, Outcome 4 subsequent intrauterine pregnancy.

Study or subgroup	laparoscopy n/N	open surgery n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Lundorff 1992	22/42	20/45		71.86%	1.37[0.59,3.16]
Vermesh 1992	13/19	15/21		28.14%	0.87[0.23,3.31]
Total (95% CI)	**61**	**66**		**100%**	**1.21[0.59,2.45]**
Total events: 35 (laparoscopy), 35 (open surgery)					
Heterogeneity: Tau^2=0; Chi^2=0.32, df=1(P=0.57); I^2=0%					
Test for overall effect: Z=0.52(P=0.61)					



Analysis 1.5. Comparison 1 laparoscopic salpingostomy versus salpingostomy by open surgery, Outcome 5 repeat ectopic pregnancy.

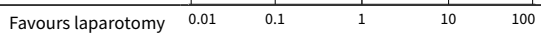
Study or subgroup	laparoscopy n/N	open surgery n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Lundorff 1992	3/42	5/45		62.12%	0.63[0.15,2.66]
Vermesh 1992	1/19	4/21		37.88%	0.29[0.05,1.87]
Total (95% CI)	**61**	**66**		**100%**	**0.47[0.15,1.47]**
Total events: 4 (laparoscopy), 9 (open surgery)					
Heterogeneity: Tau^2=0; Chi^2=0.4, df=1(P=0.53); I^2=0%					
Test for overall effect: Z=1.3(P=0.19)					

Comparison 2. minilaparotomy versus laparotomy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 primary treatment success	1	60	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 2.1. Comparison 2 minilaparotomy versus laparotomy, Outcome 1 primary treatment success.

Study or subgroup	Minila-parotomy n/N	Laparotomy n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Sharma 2003	30/30	30/30			Not estimable
Total (95% CI)	**30**	**30**			**Not estimable**
Total events: 30 (Minilaparotomy), 30 (Laparotomy)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

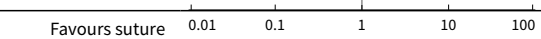


Comparison 3. salpingostomy without tubal suturing versus salpingostomy with tubal suturing

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 primary treatment success	2	109	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.16 [0.02, 1.23]
2 persistent trophoblast	2	109	Peto Odds Ratio (Peto, Fixed, 95% CI)	6.16 [0.81, 46.56]
3 tubal patency rate	1	66	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.38 [0.06, 2.35]
4 subsequent intrauterine pregnancy	2	88	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.07 [0.44, 2.57]
5 repeat ectopic pregnancy	2	88	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.20 [0.38, 3.81]

Analysis 3.1. Comparison 3 salpingostomy without tubal suturing versus salpingostomy with tubal suturing, Outcome 1 primary treatment success.

Study or subgroup	no suture n/N	suture n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Fujishita 2004	39/43	32/32		100%	0.16[0.02,1.23]
Tulandi 1991a	15/15	19/19			Not estimable
Total (95% CI)	**58**	**51**		**100%**	**0.16[0.02,1.23]**
Total events: 54 (no suture), 51 (suture)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.76(P=0.08)					



Analysis 3.2. Comparison 3 salpingostomy without tubal suturing versus salpingostomy with tubal suturing, Outcome 2 persistent trophoblast.

Study or subgroup	no suture n/N	suture n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Fujishita 2004	4/43	0/32		100%	6.16[0.81,46.56]
Tulandi 1991a	0/15	0/19			Not estimable
Total (95% CI)	**58**	**51**		**100%**	**6.16[0.81,46.56]**
Total events: 4 (no suture), 0 (suture)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.76(P=0.08)					

Analysis 3.3. Comparison 3 salpingostomy without tubal suturing versus salpingostomy with tubal suturing, Outcome 3 tubal patency rate.

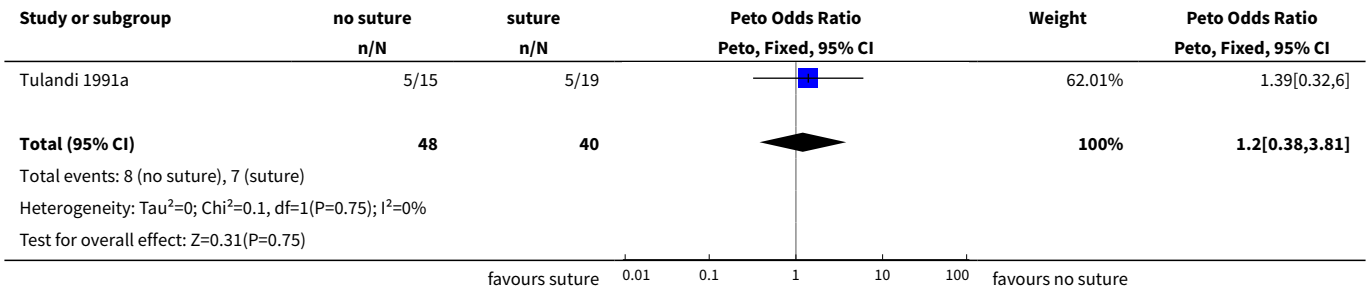
Study or subgroup	no suture n/N	suture n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Fujishita 2004	34/38	27/28		100%	0.38[0.06,2.35]
Total (95% CI)	**38**	**28**		**100%**	**0.38[0.06,2.35]**
Total events: 34 (no suture), 27 (suture)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.05(P=0.29)					

Analysis 3.4. Comparison 3 salpingostomy without tubal suturing versus salpingostomy with tubal suturing, Outcome 4 subsequent intrauterine pregnancy.

Study or subgroup	no suture n/N	suture n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Fujishita 2004	23/33	14/21		56.73%	1.15[0.36,3.69]
Tulandi 1991a	7/15	9/19		43.27%	0.97[0.26,3.7]
Total (95% CI)	**48**	**40**		**100%**	**1.07[0.44,2.57]**
Total events: 30 (no suture), 23 (suture)					
Heterogeneity: $Tau^2=0$; $Chi^2=0.03$, df=1(P=0.86); $I^2=0\%$					
Test for overall effect: Z=0.15(P=0.88)					

Analysis 3.5. Comparison 3 salpingostomy without tubal suturing versus salpingostomy with tubal suturing, Outcome 5 repeat ectopic pregnancy.

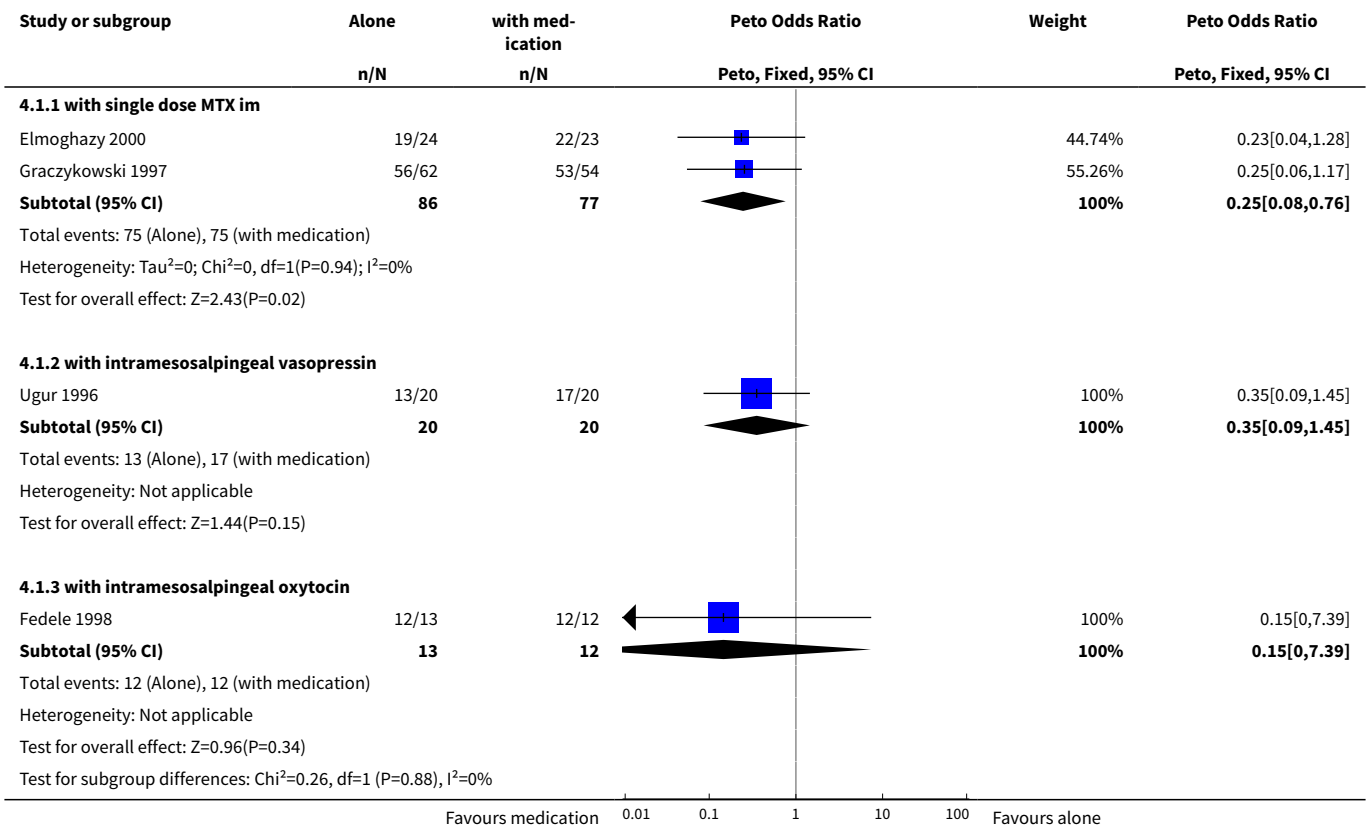
Study or subgroup	no suture n/N	suture n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Fujishita 2004	3/33	2/21		37.99%	0.95[0.15,6.17]



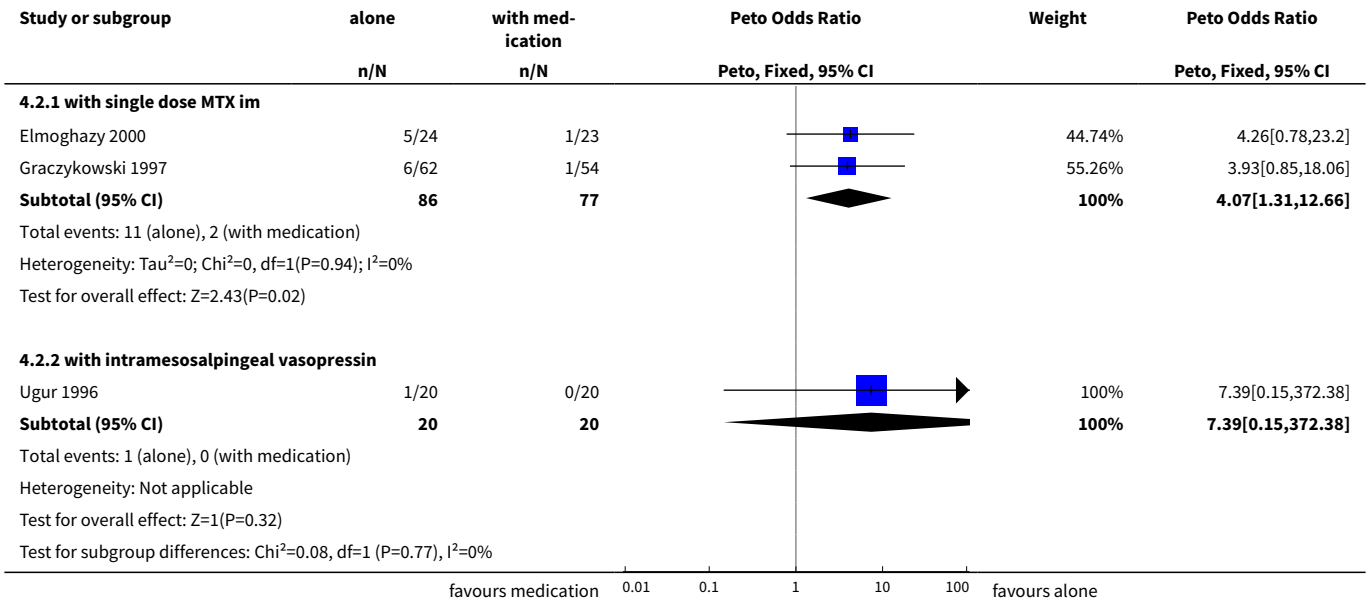
Comparison 4. salpingostomy alone versus combined with medical treatment

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 primary treatment success	4		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 with single dose MTX im	2	163	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.25 [0.08, 0.76]
1.2 with intramesosalpingeal vasopressin	1	40	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.35 [0.09, 1.45]
1.3 with intramesosalpingeal oxytocin	1	25	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.15 [0.00, 7.39]
2 persistent trophoblast	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.1 with single dose MTX im	2	163	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.07 [1.31, 12.66]
2.2 with intramesosalpingeal vasopressin	1	40	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.39 [0.15, 372.38]
3 tubal preservation	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
3.1 with single dose MTX im	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 with intramesosalpingeal vasopressin	1	40	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.64 [0.10, 4.07]
4 tubal patency	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
4.1 with intramesosalpingeal vasopressin	1	31	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.42 [0.10, 1.88]

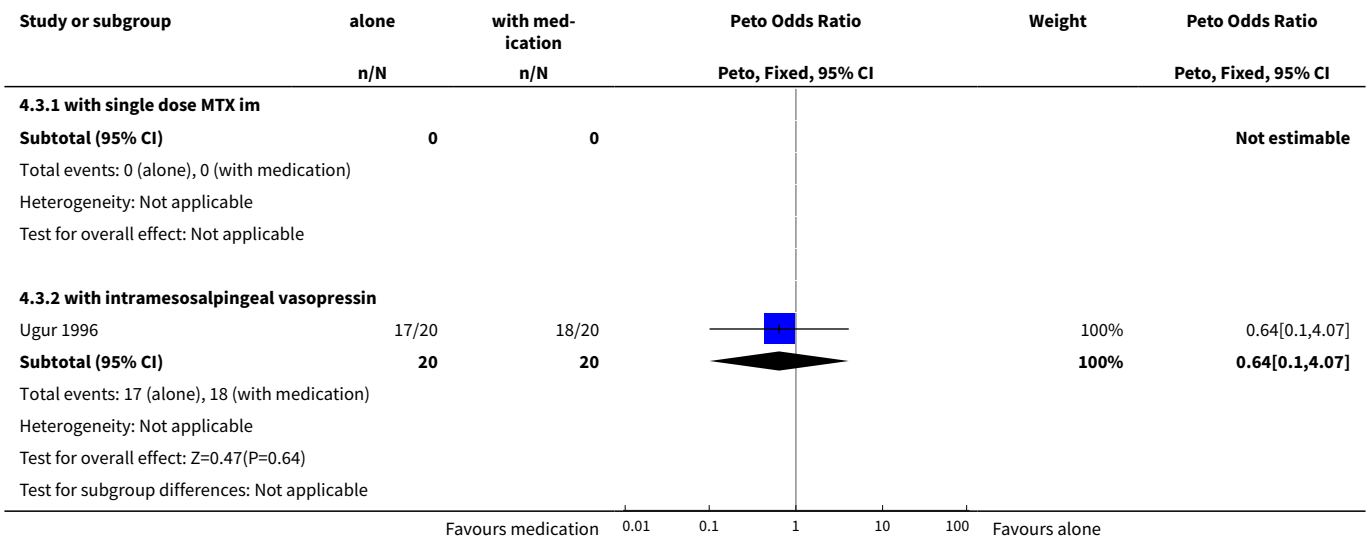
Analysis 4.1. Comparison 4 salpingostomy alone versus combined with medical treatment, Outcome 1 primary treatment success.



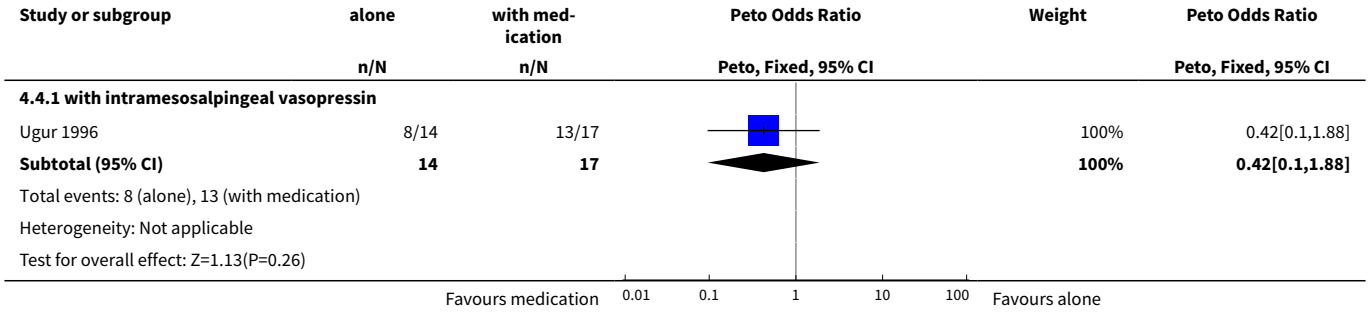
Analysis 4.2. Comparison 4 salpingostomy alone versus combined with medical treatment, Outcome 2 persistent trophoblast.



Analysis 4.3. Comparison 4 salpingostomy alone versus combined with medical treatment, Outcome 3 tubal preservation.



Analysis 4.4. Comparison 4 salpingostomy alone versus combined with medical treatment, Outcome 4 tubal patency.

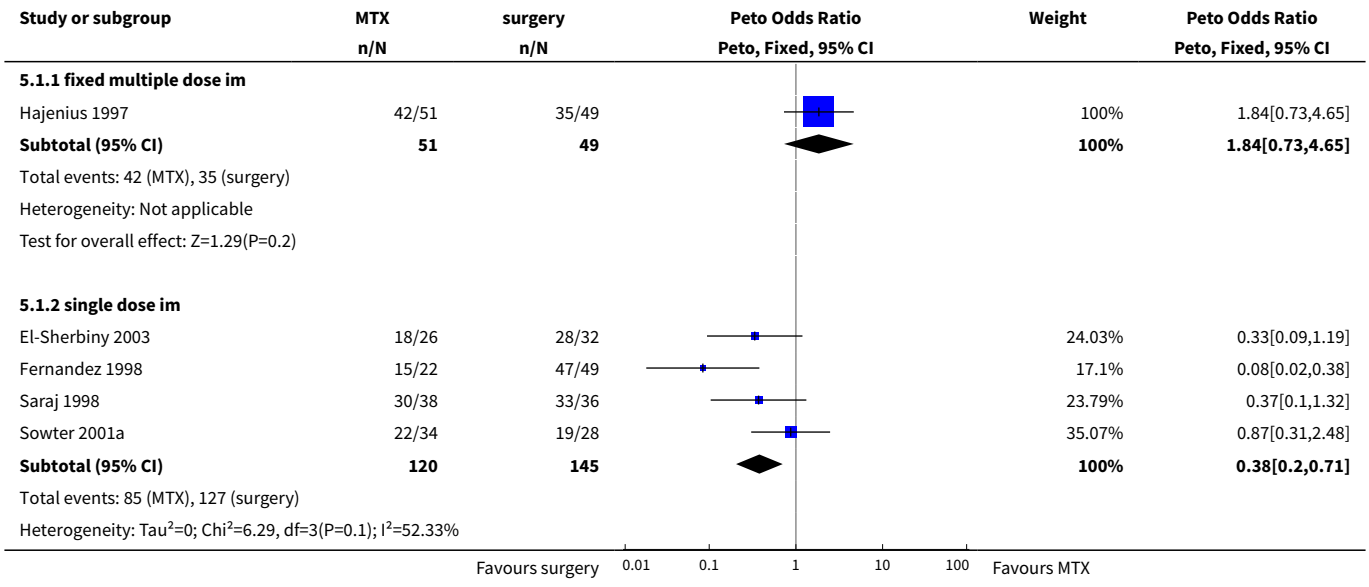


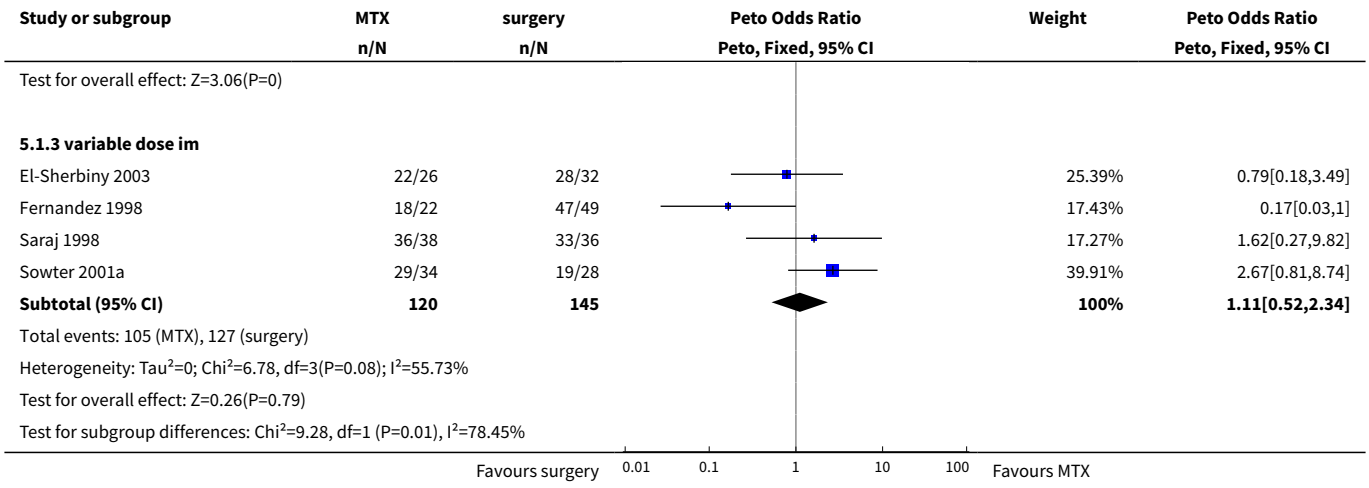
Comparison 5. Systemic MTX versus laparoscopic salpingostomy

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 primary treatment success	5		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 fixed multiple dose im	1	100	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.84 [0.73, 4.65]
1.2 single dose im	4	265	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.38 [0.20, 0.71]
1.3 variable dose im	4	265	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.11 [0.52, 2.34]
2 persistent trophoblast	5		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only

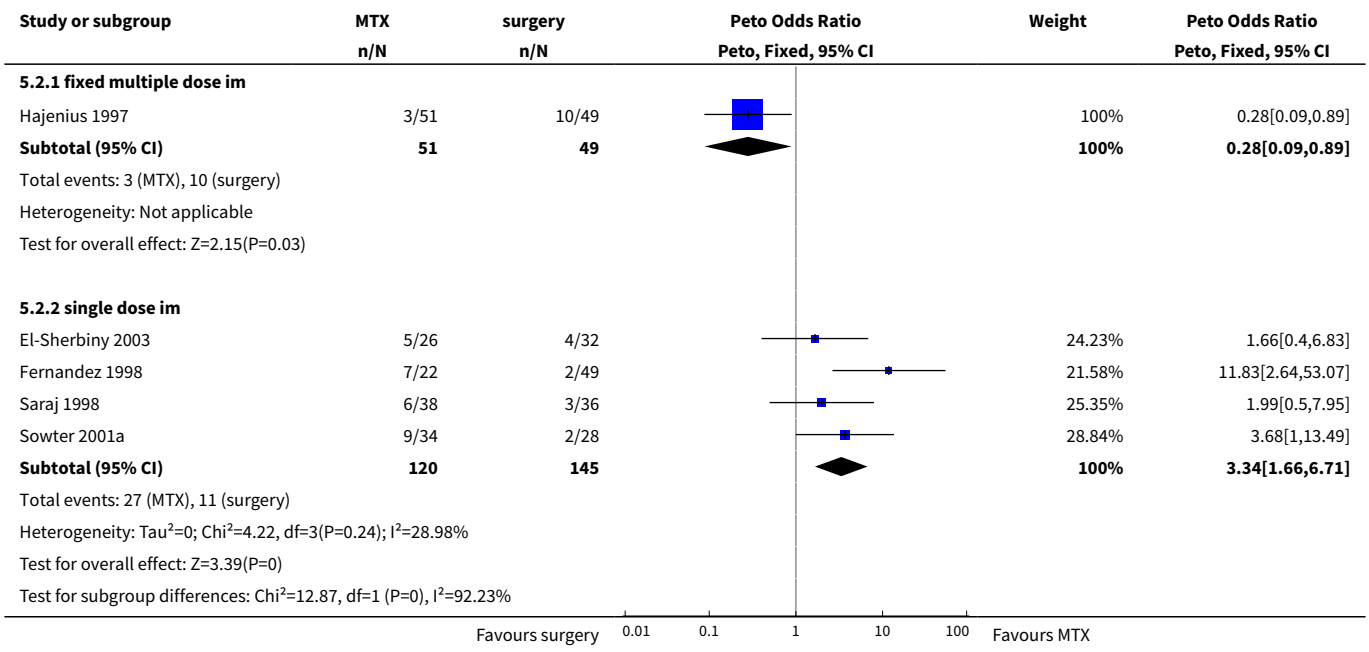
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 fixed multiple dose im	1	100	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.28 [0.09, 0.89]
2.2 single dose im	4	265	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.34 [1.66, 6.71]
3 tubal preservation	4		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
3.1 fixed multiple dose im	1	100	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.82 [0.21, 3.21]
3.3 variable dose im	3	194	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.07 [0.84, 5.08]
4 tubal patency	4		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
4.1 fixed multiple dose im	1	81	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.84 [0.35, 2.02]
4.2 variable dose im	3	115	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.47 [0.69, 3.14]
5 subsequent intra uterine pregnancy	4		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
5.1 fixed multiple dose im	1	74	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.82 [0.32, 2.09]
5.3 variable dose im	3	98	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.01 [0.43, 2.41]
6 repeat ectopic pregnancy	4		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
6.1 fixed multiple dose im	1	74	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.87 [0.19, 4.12]
6.2 variable dose im	3	98	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.54 [0.12, 2.44]

Analysis 5.1. Comparison 5 Systemic MTX versus laparoscopic salpingostomy, Outcome 1 primary treatment success.

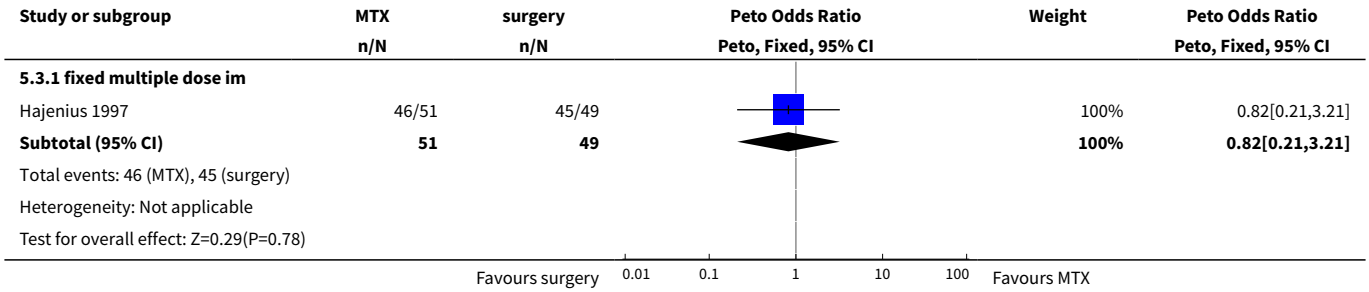


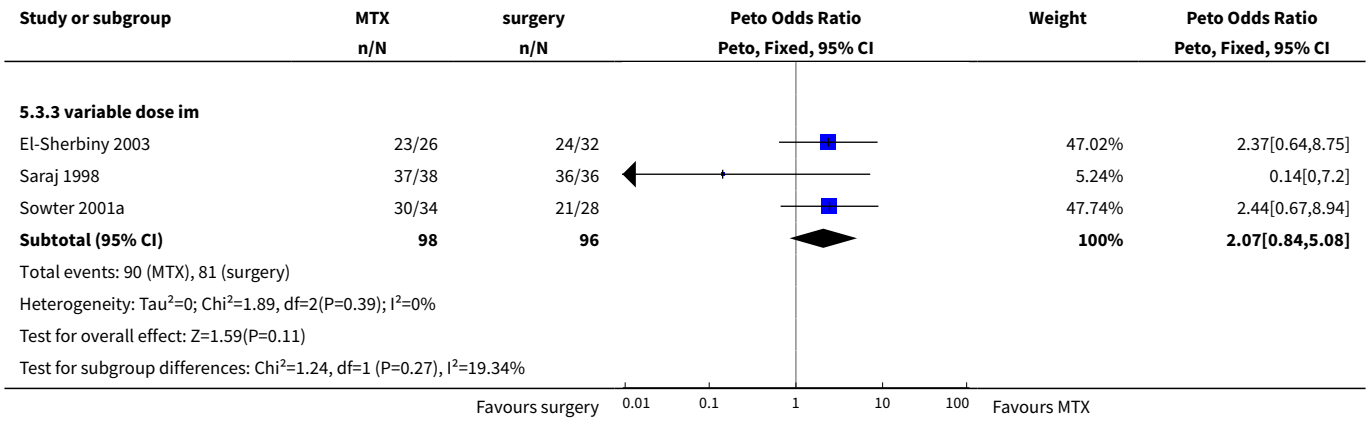


Analysis 5.2. Comparison 5 Systemic MTX versus laparoscopic salpingostomy, Outcome 2 persistent trophoblast.

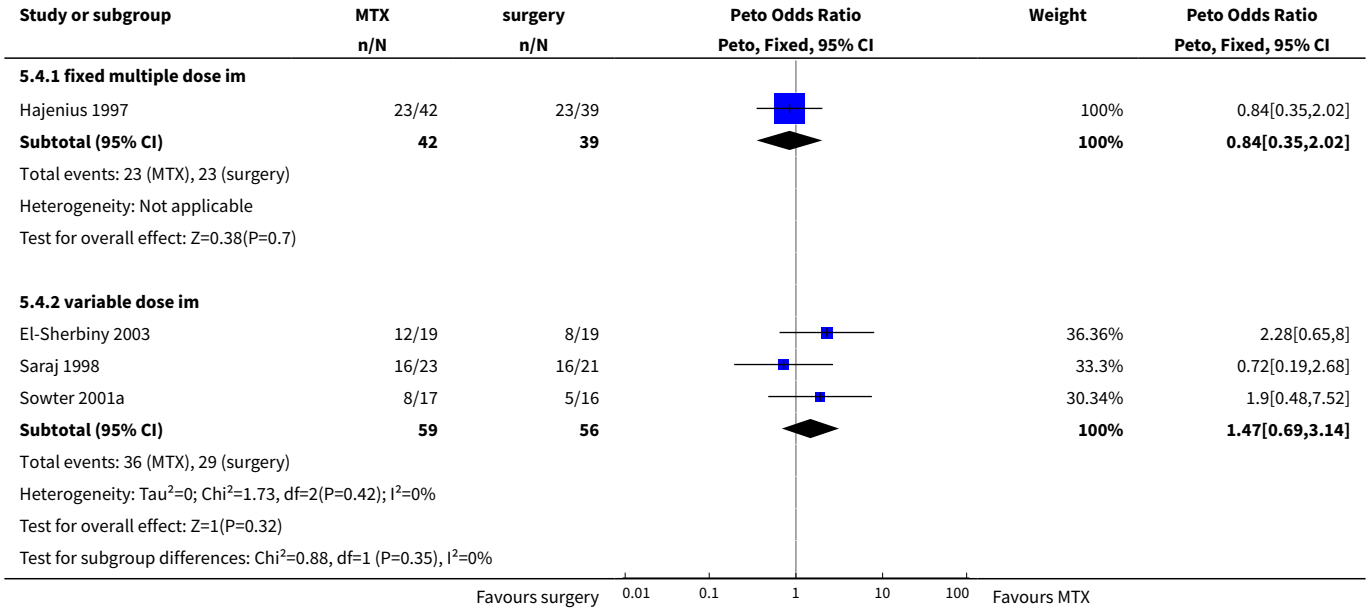


Analysis 5.3. Comparison 5 Systemic MTX versus laparoscopic salpingostomy, Outcome 3 tubal preservation.

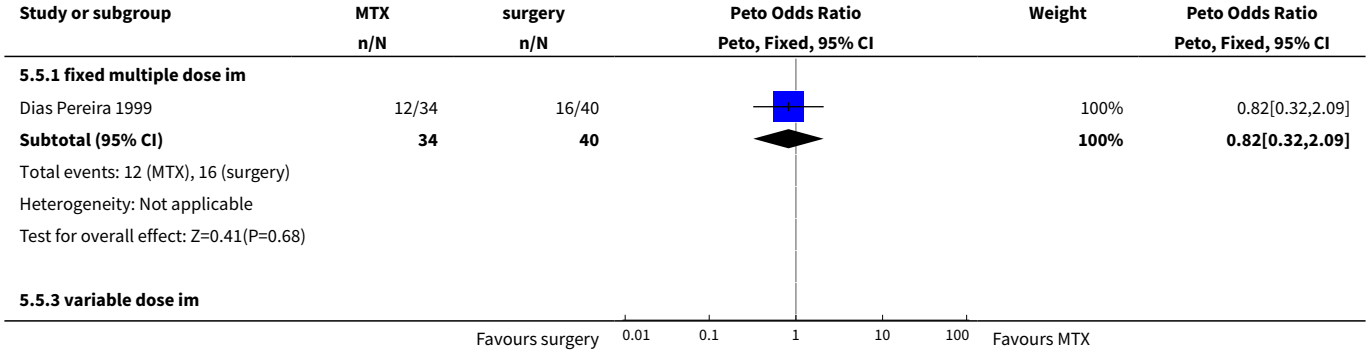


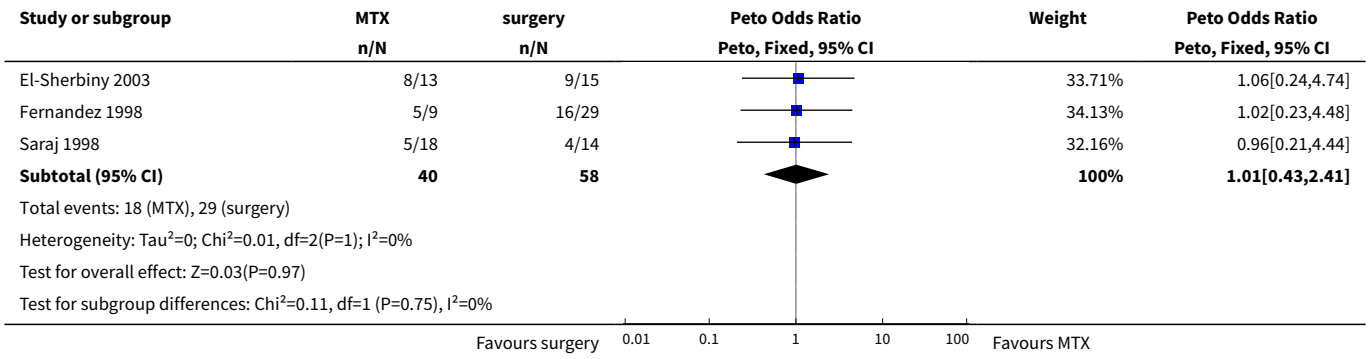


Analysis 5.4. Comparison 5 Systemic MTX versus laparoscopic salpingostomy, Outcome 4 tubal patency.

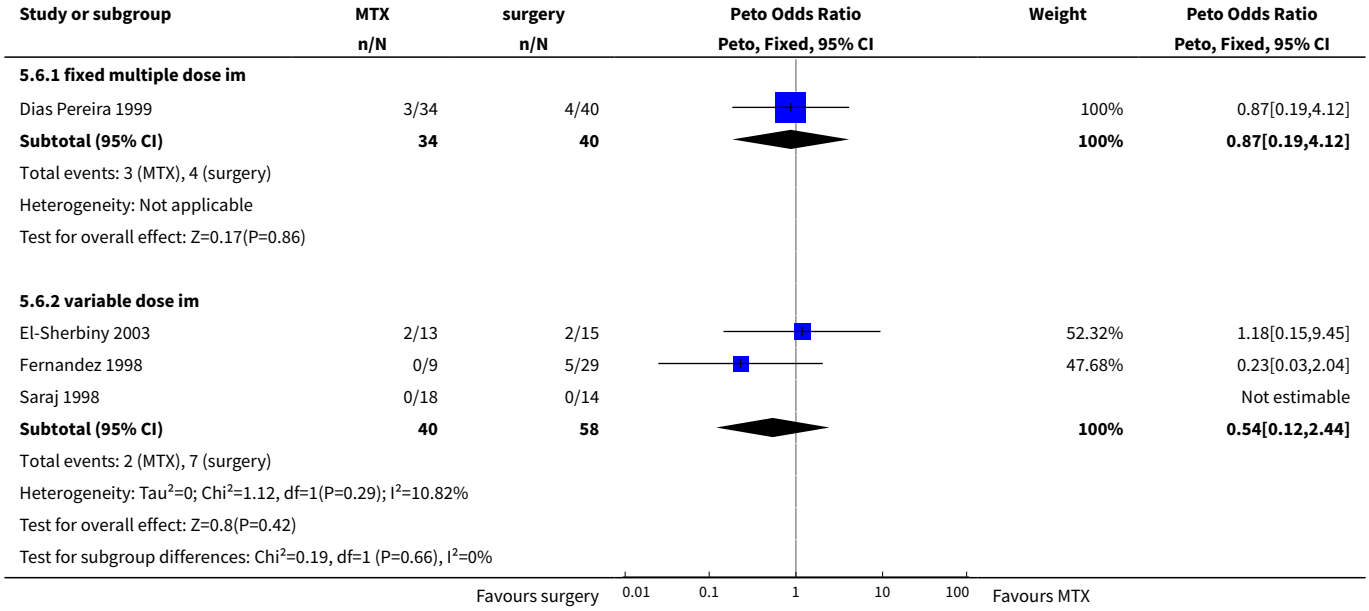


Analysis 5.5. Comparison 5 Systemic MTX versus laparoscopic salpingostomy, Outcome 5 subsequent intra uterine pregnancy.





Analysis 5.6. Comparison 5 Systemic MTX versus laparoscopic salpingostomy, Outcome 6 repeat ectopic pregnancy.



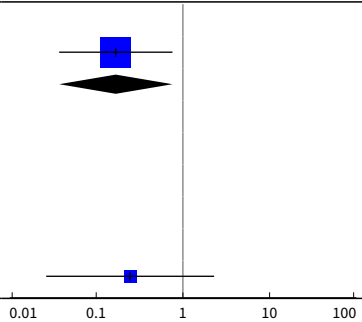
Comparison 6. local MTX versus laparoscopic salpingostomy

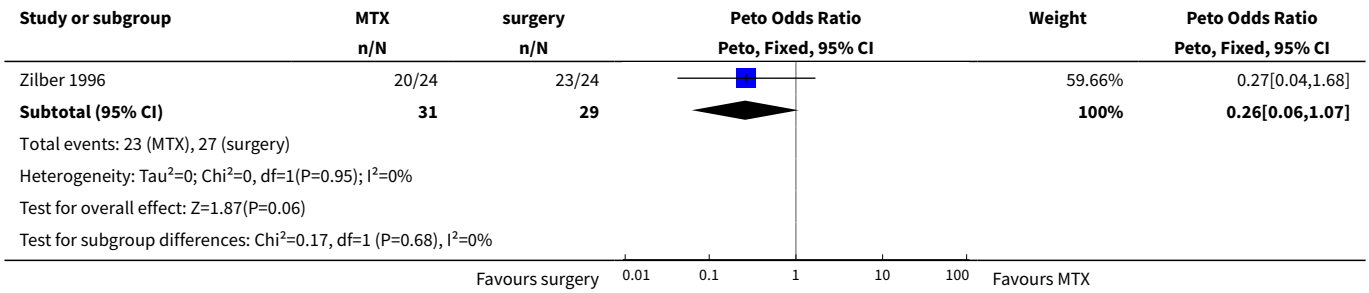
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 primary treatment success	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 transvaginally under sonographic guidance	1	78	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.17 [0.04, 0.76]
1.2 under laparoscopic guidance	2	60	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.26 [0.06, 1.07]
2 persistent trophoblast	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
2.1 transvaginally under sonographic guidance	1	78	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.91 [0.99, 24.21]
2.2 under laparoscopic guidance	2	60	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.85 [0.93, 15.85]
3 tubal preservation	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
3.1 under laparoscopic guidance	2	60	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.16 [0.01, 2.54]
4 tubal patency	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
4.1 transvaginally under sonographic guidance	1	35	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.94 [0.12, 7.32]
5 subsequent intra uterine pregnancy	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
5.1 transvaginally under sonographic guidance	1	51	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.14 [1.27, 13.50]
5.2 under laparoscopic guidance	1	34	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.87 [0.15, 4.96]
6 repeat ectopic pregnancy	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
6.1 transvaginally under sonographic guidance	1	51	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.30 [0.05, 1.66]
6.2 under laparoscopic guidance	1	34	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.15 [0.00, 7.67]

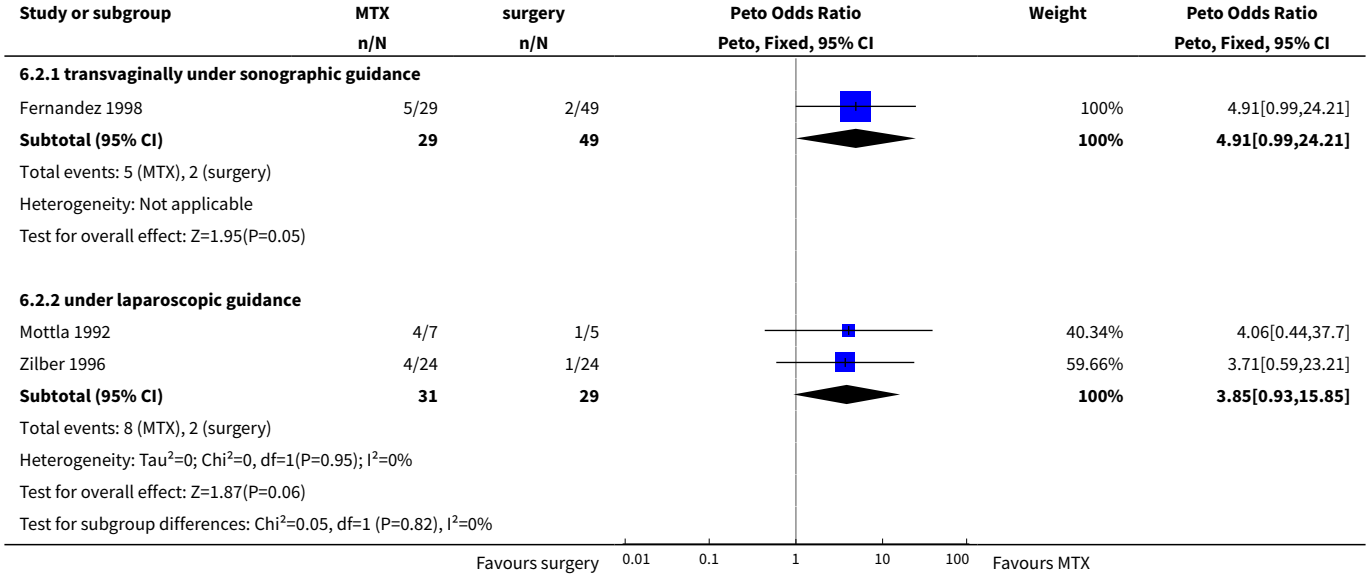
Analysis 6.1. Comparison 6 local MTX versus laparoscopic salpingostomy, Outcome 1 primary treatment success.

Study or subgroup	MTX n/N	surgery n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
6.1.1 transvaginally under sonographic guidance					
Fernandez 1998	23/29	47/49		100%	0.17[0.04,0.76]
Subtotal (95% CI)	**29**	**49**		**100%**	**0.17[0.04,0.76]**
Total events: 23 (MTX), 47 (surgery)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.32(P=0.02)					
6.1.2 under laparoscopic guidance					
Mottla 1992	3/7	4/5		40.34%	0.25[0.03,2.29]

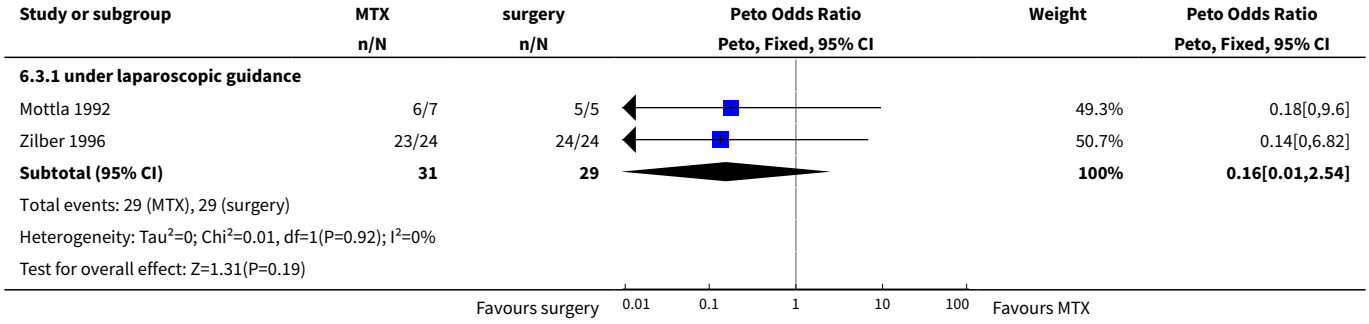




Analysis 6.2. Comparison 6 local MTX versus laparoscopic salpingostomy, Outcome 2 persistent trophoblast.

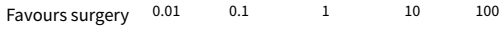


Analysis 6.3. Comparison 6 local MTX versus laparoscopic salpingostomy, Outcome 3 tubal preservation.



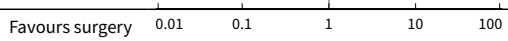
Analysis 6.4. Comparison 6 local MTX versus laparoscopic salpingostomy, Outcome 4 tubal patency.

Study or subgroup	MTX n/N	surgery n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
6.4.1 transvaginally under sonographic guidance					
Fernandez 1995	15/17	16/18		100%	0.94[0.12,7.32]
Subtotal (95% CI)	**17**	**18**		**100%**	**0.94[0.12,7.32]**
Total events: 15 (MTX), 16 (surgery)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.06(P=0.95)					



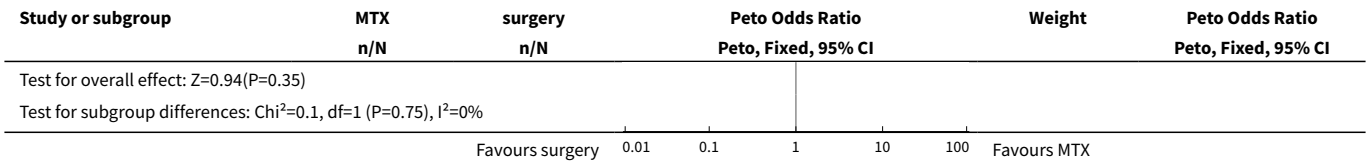
Analysis 6.5. Comparison 6 local MTX versus laparoscopic salpingostomy, Outcome 5 subsequent intra uterine pregnancy.

Study or subgroup	MTX n/N	surgery n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
6.5.1 transvaginally under sonographic guidance					
Fernandez 1998	19/22	16/29		100%	4.14[1.27,13.5]
Subtotal (95% CI)	**22**	**29**		**100%**	**4.14[1.27,13.5]**
Total events: 19 (MTX), 16 (surgery)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.35(P=0.02)					
6.5.2 under laparoscopic guidance					
Zilber 1996	13/16	15/18		100%	0.87[0.15,4.96]
Subtotal (95% CI)	**16**	**18**		**100%**	**0.87[0.15,4.96]**
Total events: 13 (MTX), 15 (surgery)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.16(P=0.88)					
Test for subgroup differences: Chi^2=2.11, df=1 (P=0.15), I^2=52.61%					



Analysis 6.6. Comparison 6 local MTX versus laparoscopic salpingostomy, Outcome 6 repeat ectopic pregnancy.

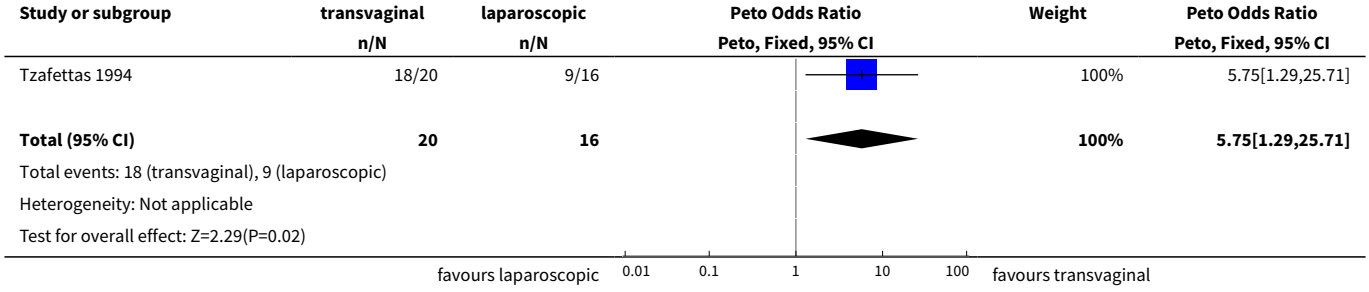
Study or subgroup	MTX n/N	surgery n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
6.6.1 transvaginally under sonographic guidance					
Fernandez 1998	1/22	5/29		100%	0.3[0.05,1.66]
Subtotal (95% CI)	**22**	**29**		**100%**	**0.3[0.05,1.66]**
Total events: 1 (MTX), 5 (surgery)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.38(P=0.17)					
6.6.2 under laparoscopic guidance					
Zilber 1996	0/16	1/18		100%	0.15[0,7.67]
Subtotal (95% CI)	**16**	**18**		**100%**	**0.15[0,7.67]**
Total events: 0 (MTX), 1 (surgery)					
Heterogeneity: Not applicable					



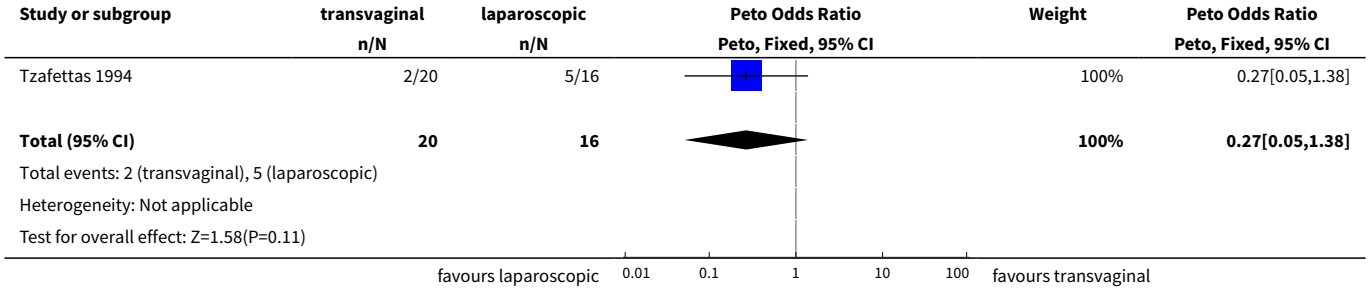
Comparison 7. MTX transvaginally under sonographic guidance versus MTX under laparoscopic guidance

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 primary treatment success	1	36	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.75 [1.29, 25.71]
2 persistent trophoblast	1	36	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.27 [0.05, 1.38]

Analysis 7.1. Comparison 7 MTX transvaginally under sonographic guidance versus MTX under laparoscopic guidance, Outcome 1 primary treatment success.



Analysis 7.2. Comparison 7 MTX transvaginally under sonographic guidance versus MTX under laparoscopic guidance, Outcome 2 persistent trophoblast.

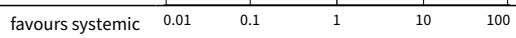


Comparison 8. MTX transvaginally under sonographic guidance versus systemic single dose MTX im

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 primary treatment success	3	95	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.14 [0.82, 5.56]
2 persistent trophoblast	3	95	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.40 [0.13, 1.18]
3 tubal preservation	1	24	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.08 [0.19, 22.17]
4 subsequent intrauterine pregnancy	2	51	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.52 [0.43, 5.31]
5 repeat ectopic pregnancy	1	31	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.09 [0.05, 307.06]

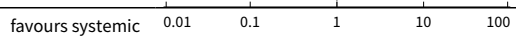
Analysis 8.1. Comparison 8 MTX transvaginally under sonographic guidance versus systemic single dose MTX im, Outcome 1 primary treatment success.

Study or subgroup	transvaginal n/N	systemic n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Cohen 1996	9/11	5/9		26.04%	3.28[0.5,21.37]
Fernandez 1994	11/12	10/12		16.29%	2.08[0.19,22.17]
Fernandez 1998	23/29	15/22		57.67%	1.78[0.5,6.26]
Total (95% CI)	**52**	**43**		**100%**	**2.14[0.82,5.56]**
Total events: 43 (transvaginal), 30 (systemic)					
Heterogeneity: Tau^2=0; Chi^2=0.28, df=2(P=0.87); I^2=0%					
Test for overall effect: Z=1.56(P=0.12)					

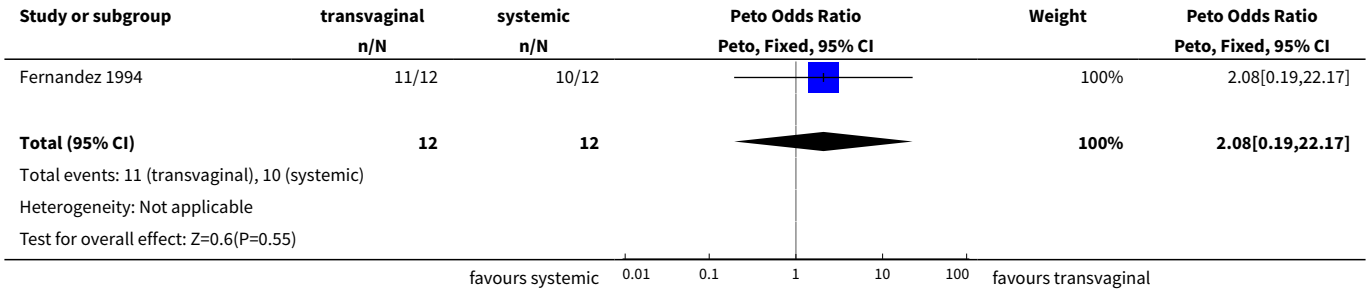


Analysis 8.2. Comparison 8 MTX transvaginally under sonographic guidance versus systemic single dose MTX im, Outcome 2 persistent trophoblast.

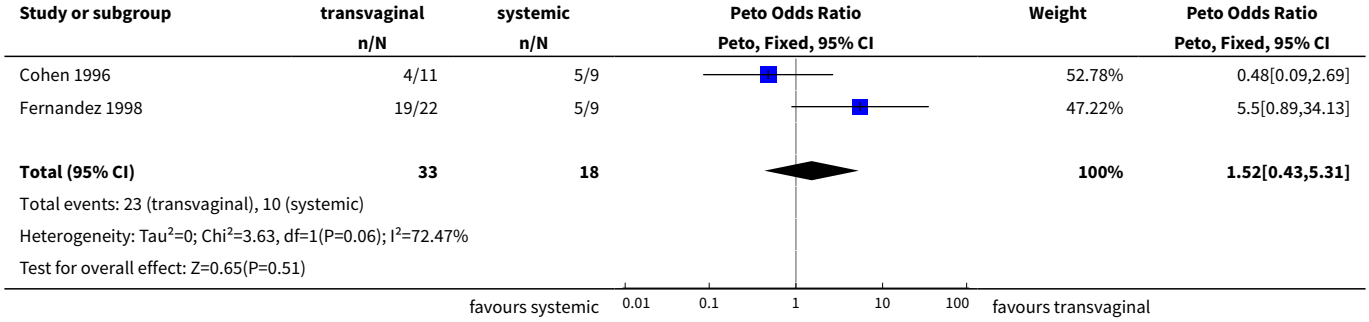
Study or subgroup	transvaginal n/N	systemic n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Cohen 1996	1/11	2/9		20.69%	0.38[0.03,4.16]
Fernandez 1994	0/12	1/12		7.79%	0.14[0,6.82]
Fernandez 1998	5/29	7/22		71.52%	0.45[0.12,1.65]
Total (95% CI)	**52**	**43**		**100%**	**0.4[0.13,1.18]**
Total events: 6 (transvaginal), 10 (systemic)					
Heterogeneity: Tau^2=0; Chi^2=0.33, df=2(P=0.85); I^2=0%					
Test for overall effect: Z=1.66(P=0.1)					



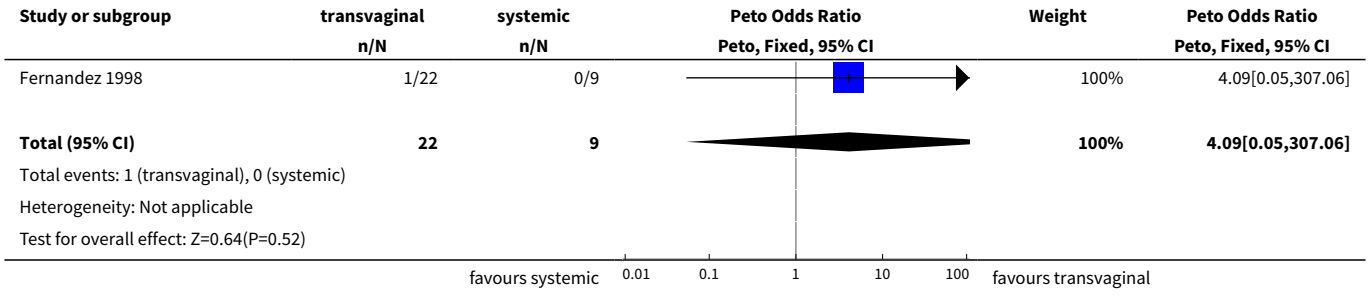
Analysis 8.3. Comparison 8 MTX transvaginally under sonographic guidance versus systemic single dose MTX im, Outcome 3 tubal preservation.



Analysis 8.4. Comparison 8 MTX transvaginally under sonographic guidance versus systemic single dose MTX im, Outcome 4 subsequent intrauterine pregnancy.



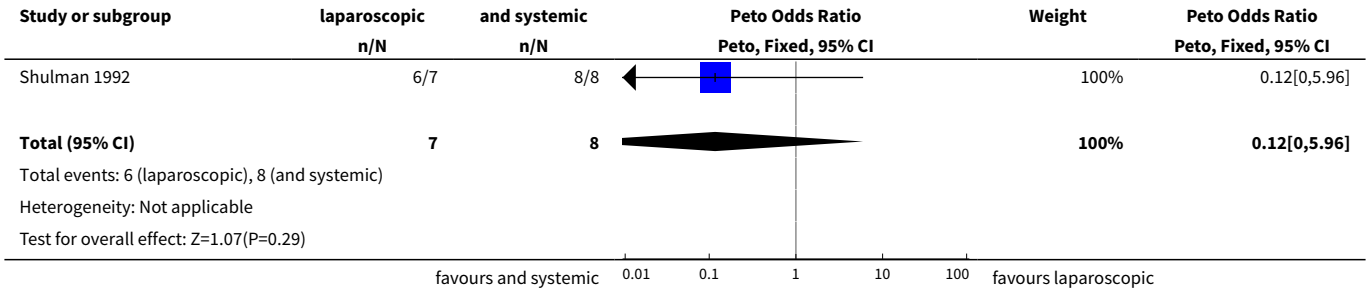
Analysis 8.5. Comparison 8 MTX transvaginally under sonographic guidance versus systemic single dose MTX im, Outcome 5 repeat ectopic pregnancy.



Comparison 9. MTX under laparoscopic guidance versus the same regimen in combination with systemic MTX im

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 primary treatment success	1	15	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.12 [0.00, 5.96]

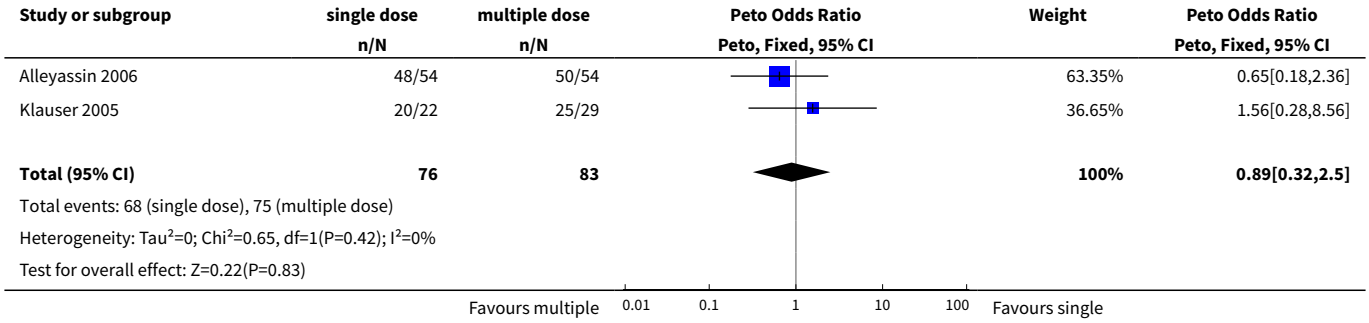
Analysis 9.1. Comparison 9 MTX under laparoscopic guidance versus the same regimen in combination with systemic MTX im, Outcome 1 primary treatment success.



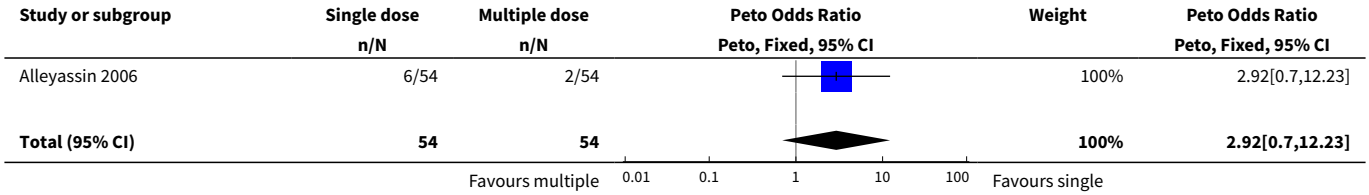
Comparison 10. single dose MTX versus fixed multiple dose MTX both im

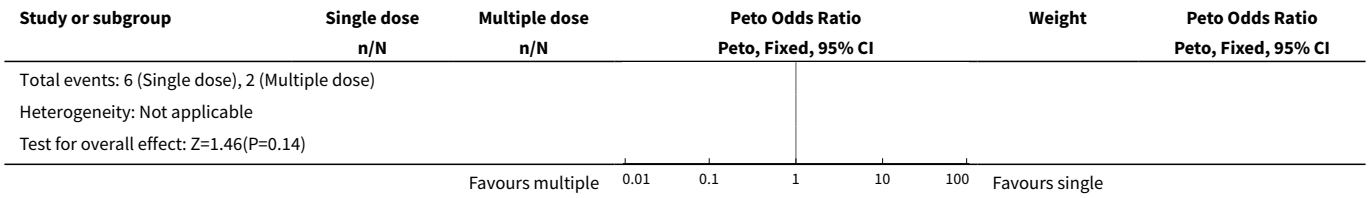
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 primary treatment success	2	159	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.89 [0.32, 2.50]
2 persistent trophoblast	1	108	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.92 [0.70, 12.23]

Analysis 10.1. Comparison 10 single dose MTX versus fixed multiple dose MTX both im, Outcome 1 primary treatment success.



Analysis 10.2. Comparison 10 single dose MTX versus fixed multiple dose MTX both im, Outcome 2 persistent trophoblast.

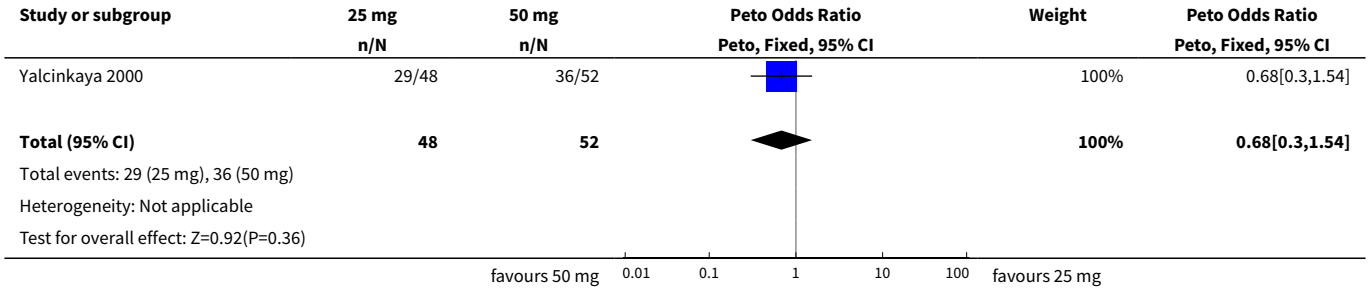




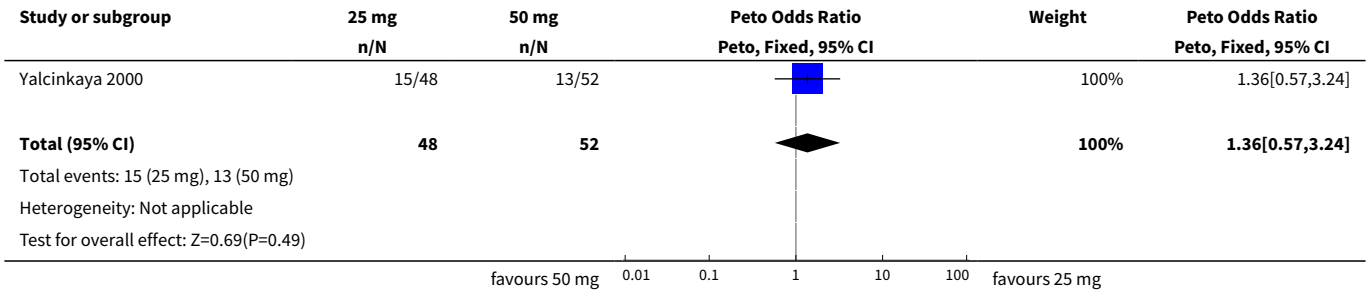
Comparison 11. 25 mg/m2 versus the standard 50 mg/m2 MTX both single dose im

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 primary treatment success	1	100	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.68 [0.30, 1.54]
2 persistent trophoblast	1	100	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.36 [0.57, 3.24]
3 treatment success with variable MTX dose	1	100	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.77 [0.24, 2.45]
4 tubal preservation	1	100	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.45 [0.09, 2.35]
5 tubal patency	1	37	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.90 [0.25, 3.22]
6 subsequent intra uterine pregnancy	1	56	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.08 [0.37, 3.16]
7 repeat ectopic pregnancy	1	56	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.56 [0.10, 3.01]

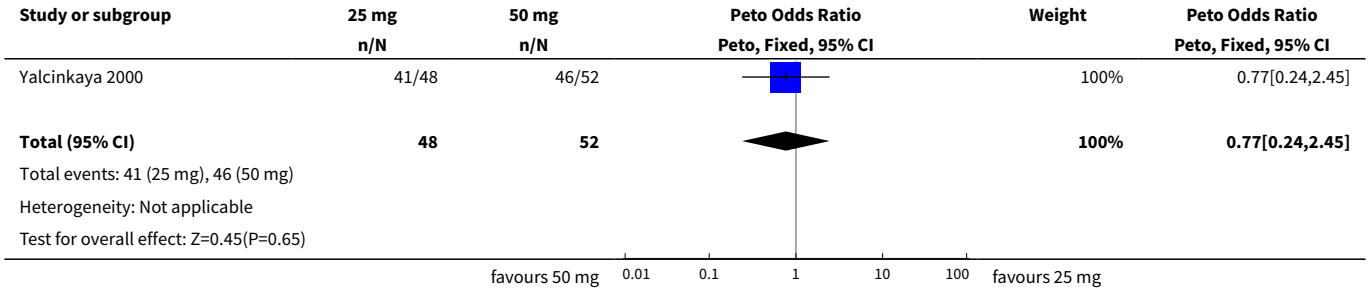
Analysis 11.1. Comparison 11 25 mg/m2 versus the standard 50 mg/m2 MTX both single dose im, Outcome 1 primary treatment success.



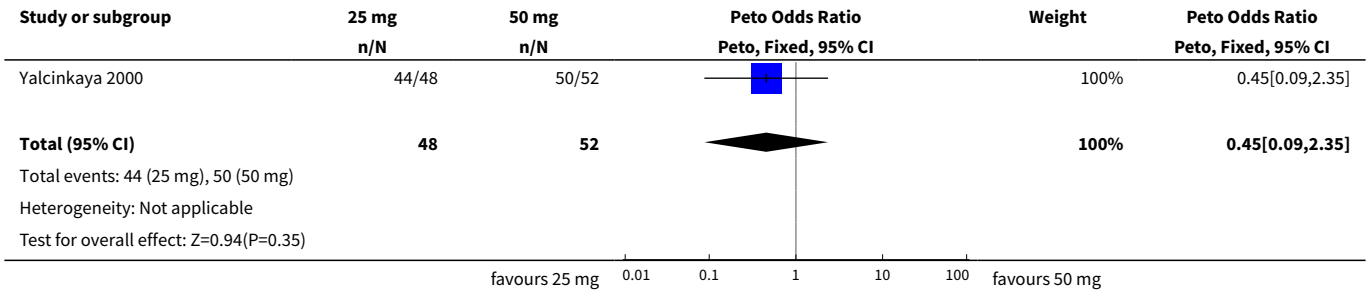
Analysis 11.2. Comparison 11 25 mg/m2 versus the standard 50 mg/m2 MTX both single dose im, Outcome 2 persistent trophoblast.



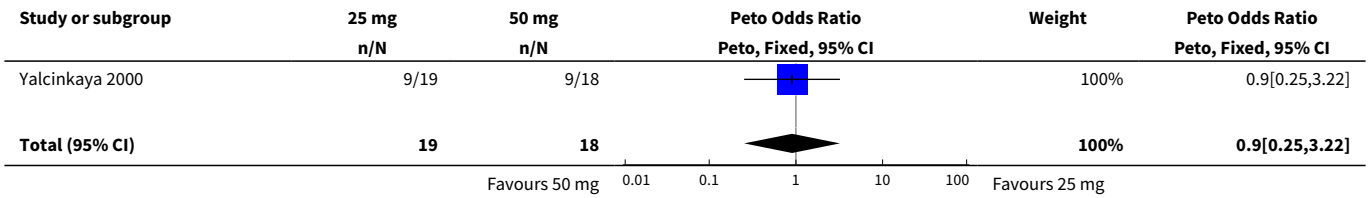
Analysis 11.3. Comparison 11 25 mg/m2 versus the standard 50 mg/m2 MTX both single dose im, Outcome 3 treatment success with variable MTX dose.

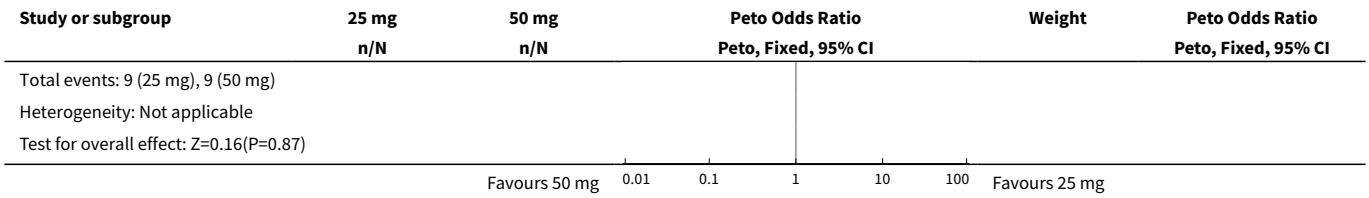


Analysis 11.4. Comparison 11 25 mg/m2 versus the standard 50 mg/m2 MTX both single dose im, Outcome 4 tubal preservation.

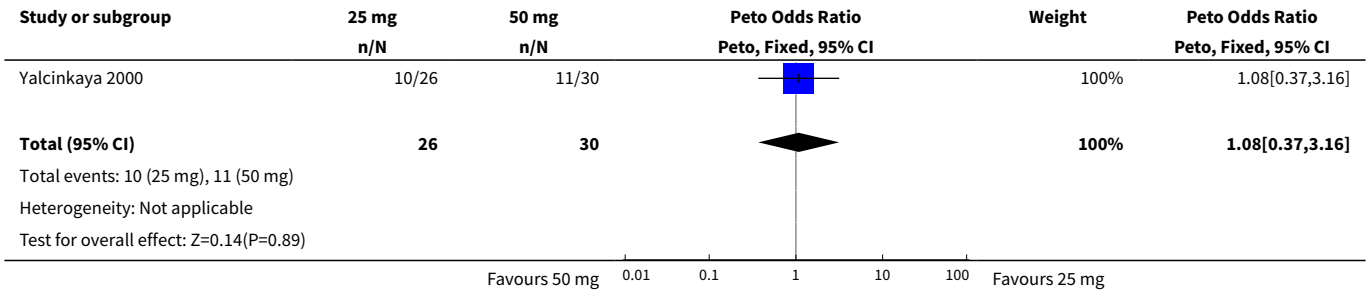


Analysis 11.5. Comparison 11 25 mg/m2 versus the standard 50 mg/m2 MTX both single dose im, Outcome 5 tubal patency.

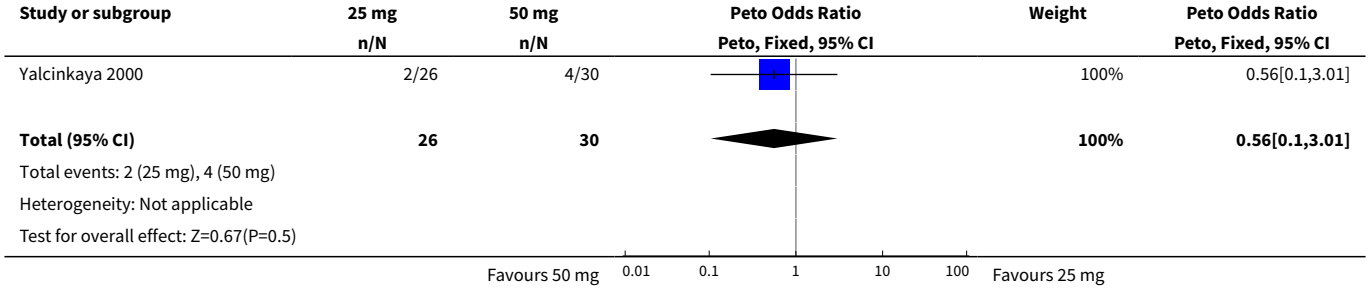




Analysis 11.6. Comparison 11 25 mg/m2 versus the standard 50 mg/m2 MTX both single dose im, Outcome 6 subsequent intra uterine pregnancy.



Analysis 11.7. Comparison 11 25 mg/m2 versus the standard 50 mg/m2 MTX both single dose im, Outcome 7 repeat ectopic pregnancy.

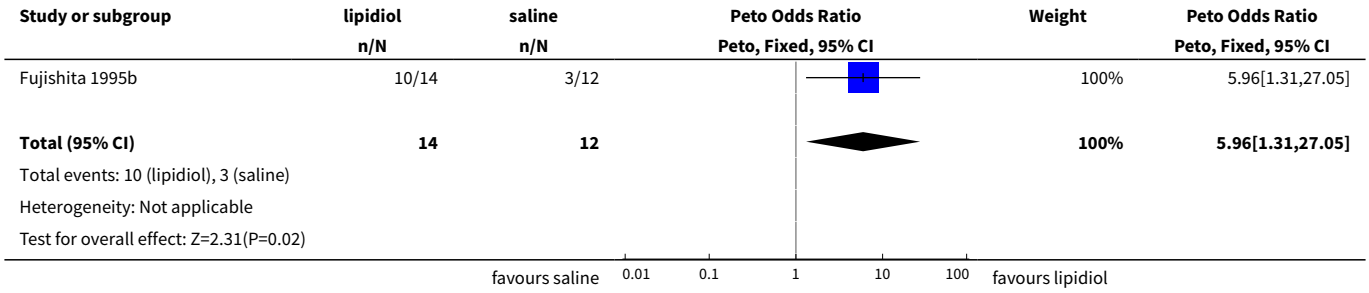


Comparison 12. MTX in lipiodol suspensions versus MTX in saline both under laparoscopic guidance

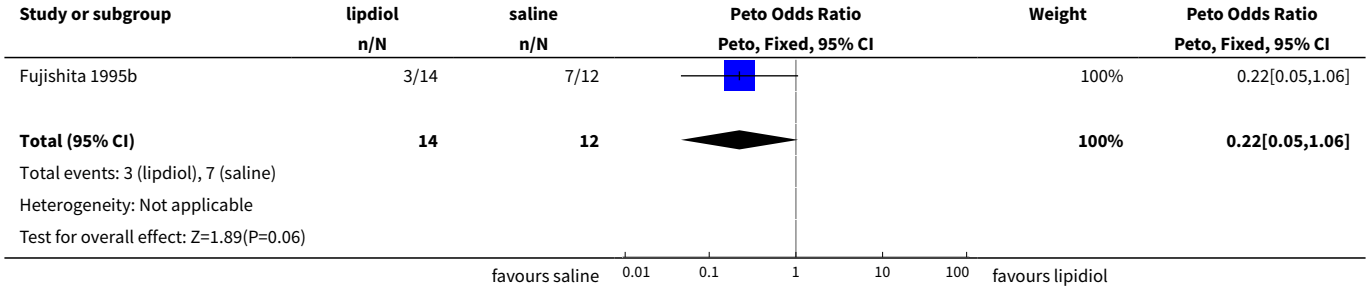
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 primary treatment success	1	26	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.96 [1.31, 27.05]
2 persistent trophoblast	1	26	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.22 [0.05, 1.06]
3 tubal preservation	1	26	Peto Odds Ratio (Peto, Fixed, 95% CI)	9.55 [0.56, 163.09]
4 tubal patency	1	22	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.06 [0.29, 14.60]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 subsequent intrauterine pregnancy	1	18	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.43 [0.07, 2.60]

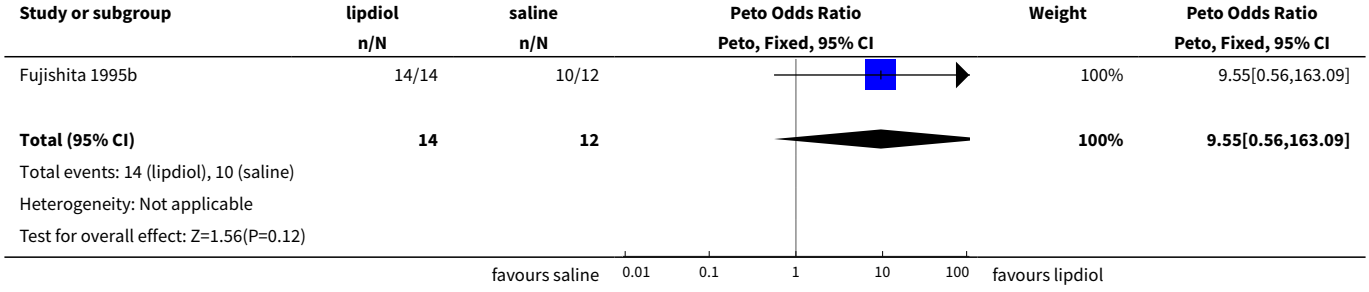
Analysis 12.1. Comparison 12 MTX in lipiodol suspensions versus MTX in saline both under laparoscopic guidance, Outcome 1 primary treatment success.



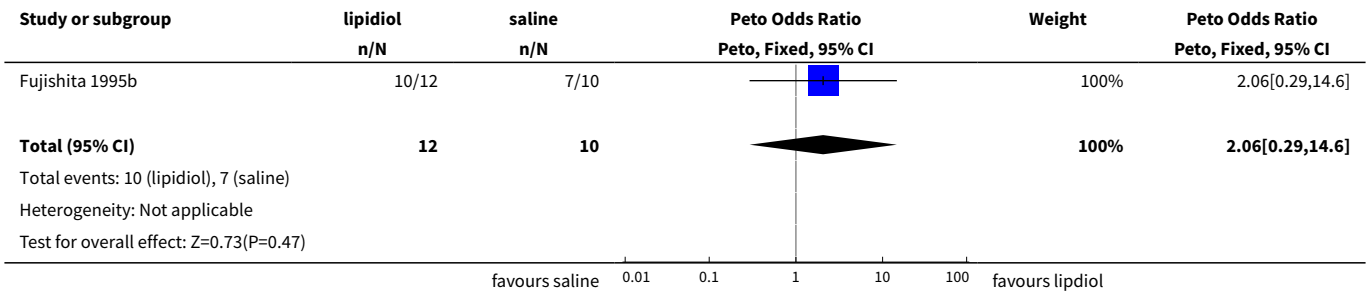
Analysis 12.2. Comparison 12 MTX in lipiodol suspensions versus MTX in saline both under laparoscopic guidance, Outcome 2 persistent trophoblast.



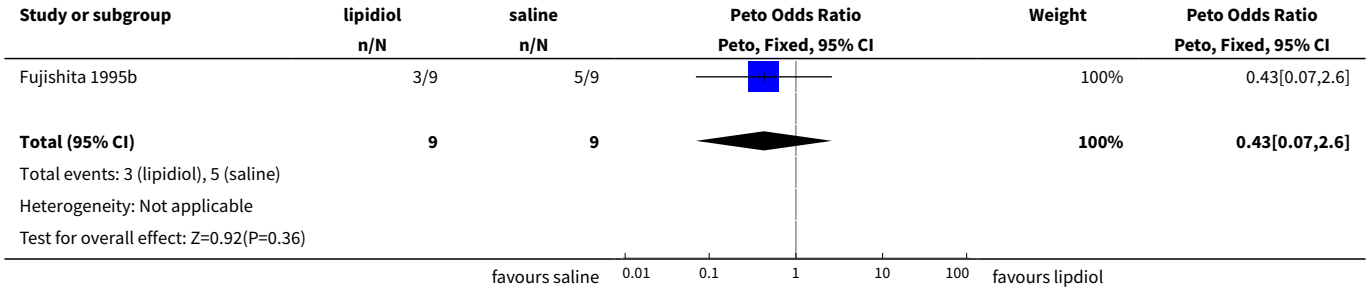
Analysis 12.3. Comparison 12 MTX in lipiodol suspensions versus MTX in saline both under laparoscopic guidance, Outcome 3 tubal preservation.



Analysis 12.4. Comparison 12 MTX in lipiodol suspensions versus MTX in saline both under laparoscopic guidance, Outcome 4 tubal patency.



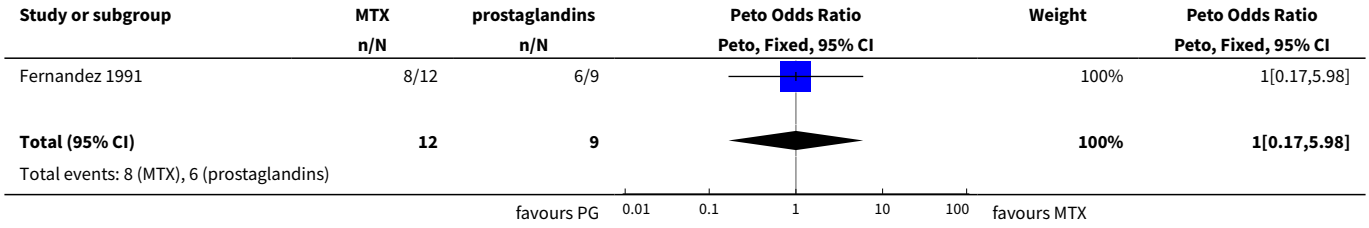
Analysis 12.5. Comparison 12 MTX in lipiodol suspensions versus MTX in saline both under laparoscopic guidance, Outcome 5 subsequent intrauterine pregnancy.

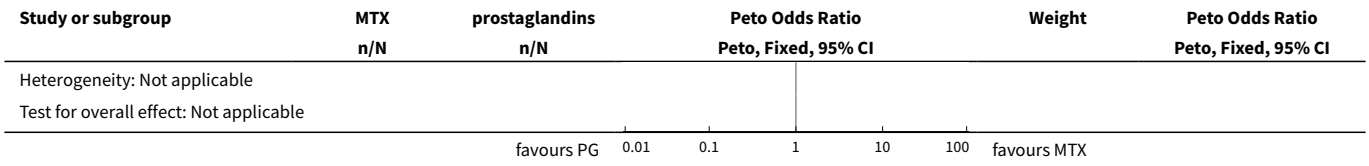


Comparison 13. MTX versus prostaglandins both under sonographic guidance combined with systemic administration of the drug

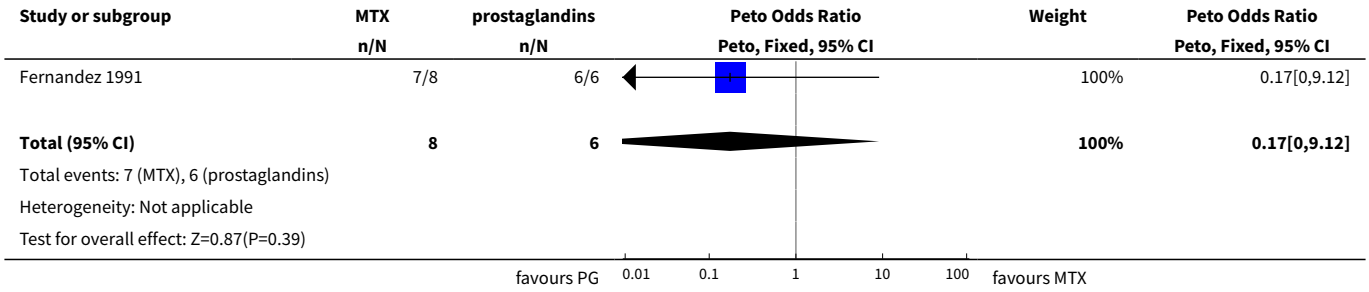
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 primary treatment success	1	21	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.0 [0.17, 5.98]
2 tubal patency	1	14	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.17 [0.00, 9.12]

Analysis 13.1. Comparison 13 MTX versus prostaglandins both under sonographic guidance combined with systemic administration of the drug, Outcome 1 primary treatment success.





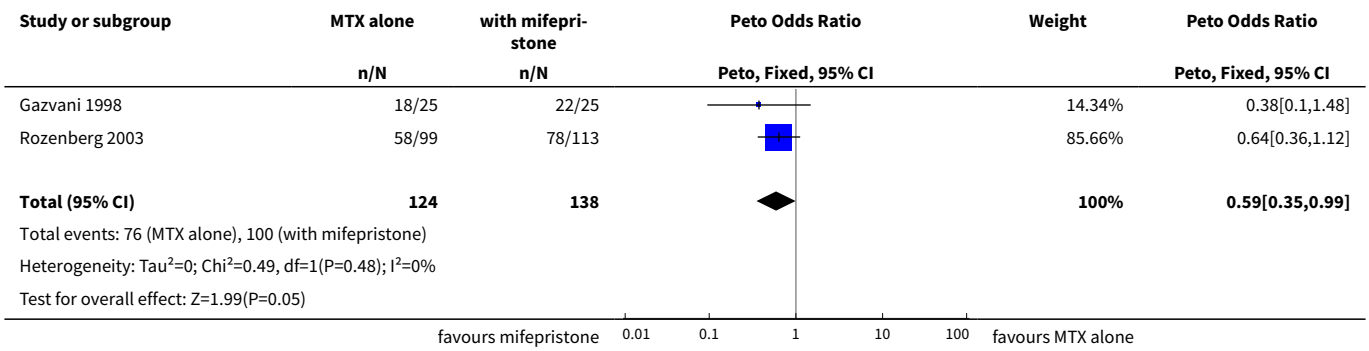
Analysis 13.2. Comparison 13 MTX versus prostaglandins both under sonographic guidance combined with systemic administration of the drug, Outcome 2 tubal patency.



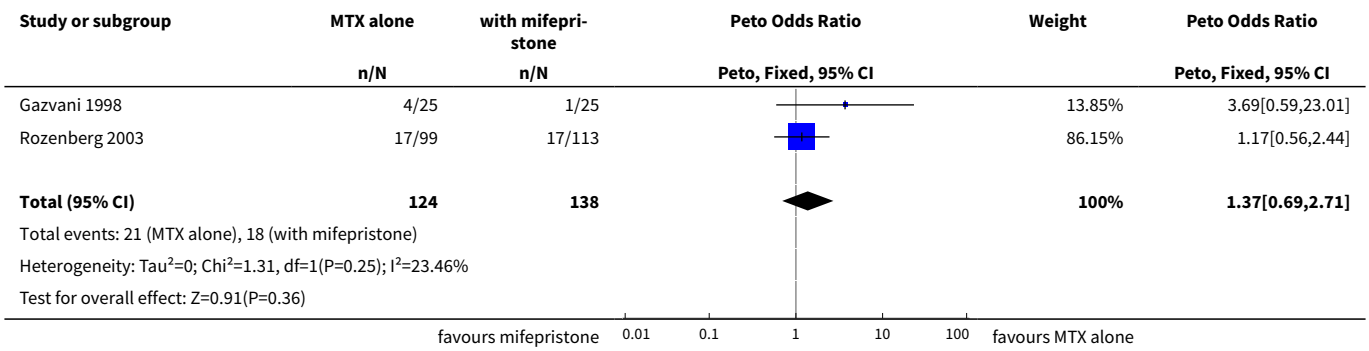
Comparison 14. single dose systemic MTX im alone versus in combination with oral mifepristone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 primary treament success	2	262	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.59 [0.35, 0.99]
2 persistent trophoblast	2	262	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.37 [0.69, 2.71]
3 tubal preservation	2	262	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.73 [0.37, 1.42]
4 tubal patency	1	24	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.38 [0.05, 3.14]

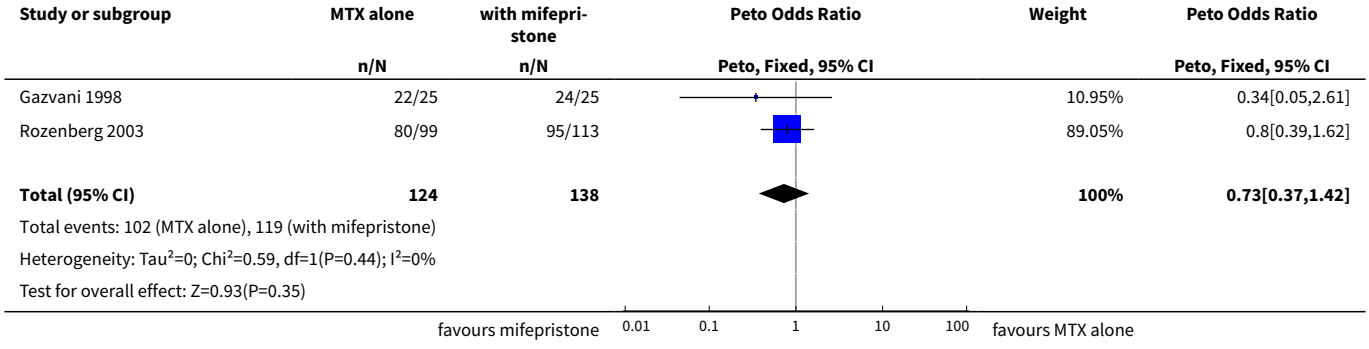
Analysis 14.1. Comparison 14 single dose systemic MTX im alone versus in combination with oral mifepristone, Outcome 1 primary treament success.



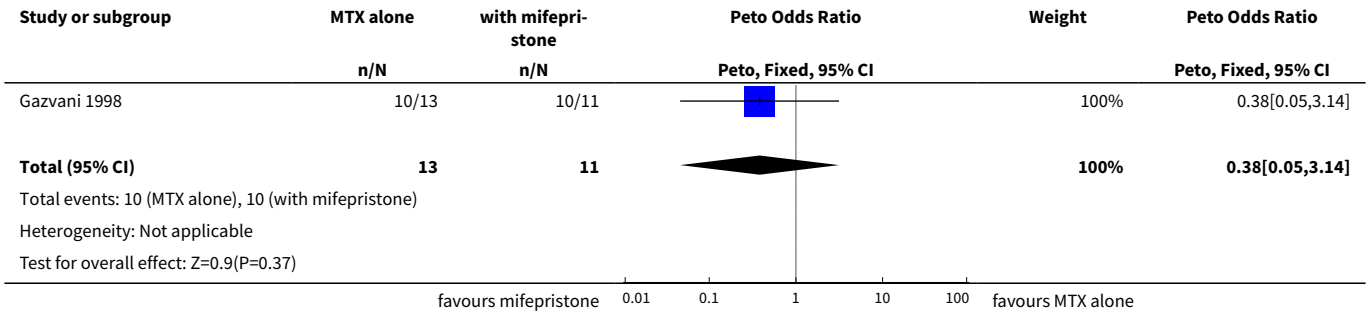
Analysis 14.2. Comparison 14 single dose systemic MTX im alone versus in combination with oral mifepristone, Outcome 2 persistent trophoblast.



Analysis 14.3. Comparison 14 single dose systemic MTX im alone versus in combination with oral mifepristone, Outcome 3 tubal preservation.



Analysis 14.4. Comparison 14 single dose systemic MTX im alone versus in combination with oral mifepristone, Outcome 4 tubal patency.

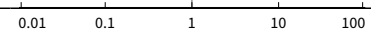


Comparison 15. single dose systemic MTX im alone versus in combination with EP2

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 primary treatment success	1	78	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.08 [0.02, 0.39]
2 subsequent intra uterine pregnancy	1	78	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.19 [0.07, 0.51]
3 repeat ectopic pregnancy	1	78	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.18 [0.74, 23.45]

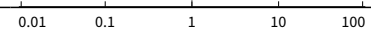
Analysis 15.1. Comparison 15 single dose systemic MTX im alone versus in combination with EP2, Outcome 1 primary treatment success.

Study or subgroup	MTX alone n/N	with EP2 n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Wang 1998	21/28	49/50		100%	0.08[0.02,0.39]
Total (95% CI)	**28**	**50**		**100%**	**0.08[0.02,0.39]**
Total events: 21 (MTX alone), 49 (with EP2)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.19(P=0)					



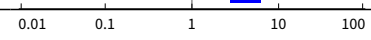
Analysis 15.2. Comparison 15 single dose systemic MTX im alone versus in combination with EP2, Outcome 2 subsequent intra uterine pregnancy.

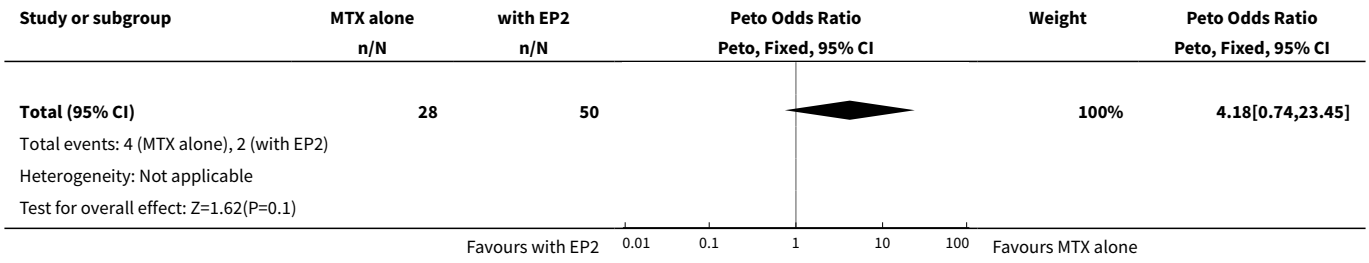
Study or subgroup	MTX alone n/N	with EP2 n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Wang 1998	12/28	40/50		100%	0.19[0.07,0.51]
Total (95% CI)	**28**	**50**		**100%**	**0.19[0.07,0.51]**
Total events: 12 (MTX alone), 40 (with EP2)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.32(P=0)					



Analysis 15.3. Comparison 15 single dose systemic MTX im alone versus in combination with EP2, Outcome 3 repeat ectopic pregnancy.

Study or subgroup	MTX alone n/N	with EP2 n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Wang 1998	4/28	2/50		100%	4.18[0.74,23.45]



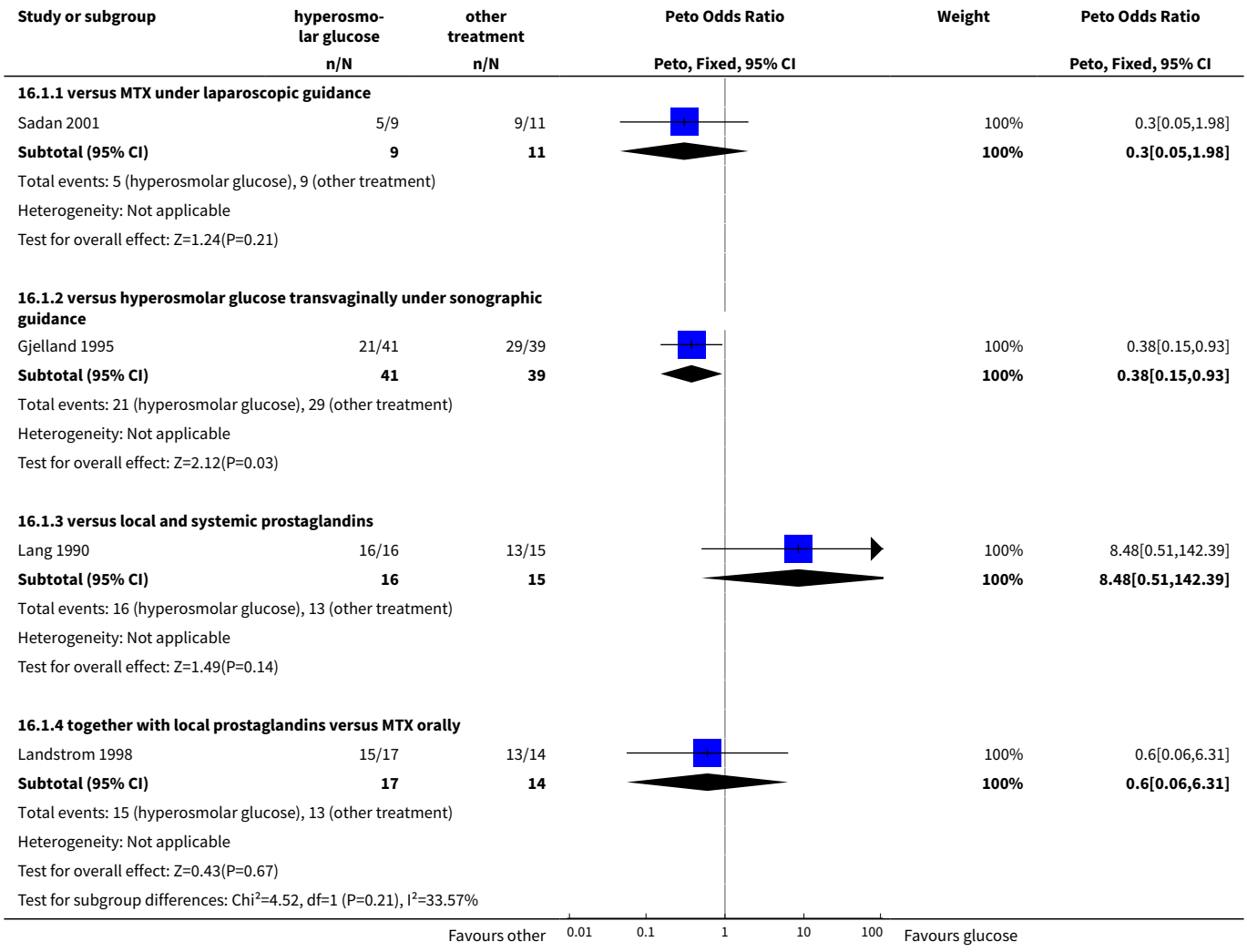


Comparison 16. hyperosmolar glucose under laparoscopic guidance versus other treatments

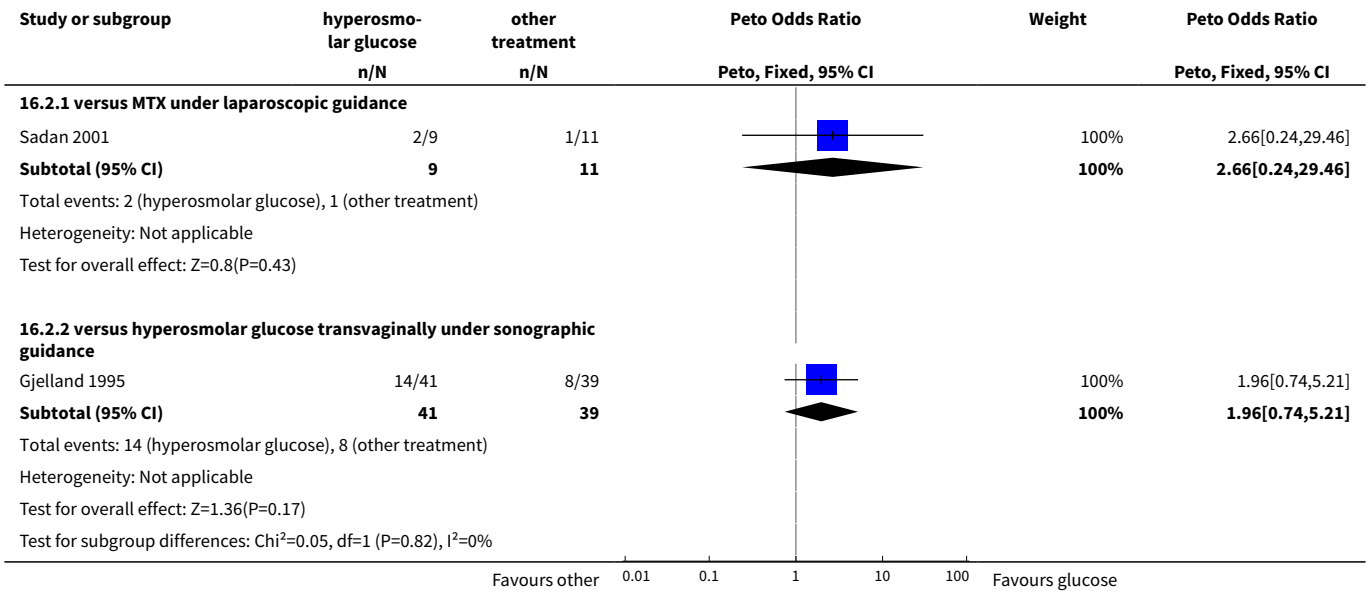
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 primary treatment success	4		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 versus MTX under laparoscopic guidance	1	20	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.30 [0.05, 1.98]
1.2 versus hyperosmolar glucose transvaginally under sonographic guidance	1	80	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.38 [0.15, 0.93]
1.3 versus local and systemic prostaglandins	1	31	Peto Odds Ratio (Peto, Fixed, 95% CI)	8.48 [0.51, 142.39]
1.4 together with local prostaglandins versus MTX orally	1	31	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.60 [0.06, 6.31]
2 persistent trofoblast	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.1 versus MTX under laparoscopic guidance	1	20	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.66 [0.24, 29.46]
2.2 versus hyperosmolar glucose transvaginally under sonographic guidance	1	80	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.96 [0.74, 5.21]
3 tubal patency	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
3.1 versus local and systemic prostaglandins	1	14	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.73 [0.04, 13.45]
4 subsequent intra uterine pregnancy	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
4.1 versus hyperosmolar glucose transvaginally under sonographic guidance	1	36	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.29 [0.88, 12.35]
5 repeat ectopic pregnancy	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 versus hyperosmolar glucose transvaginally under sonographic guidance	1	36	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.73 [0.29, 10.16]

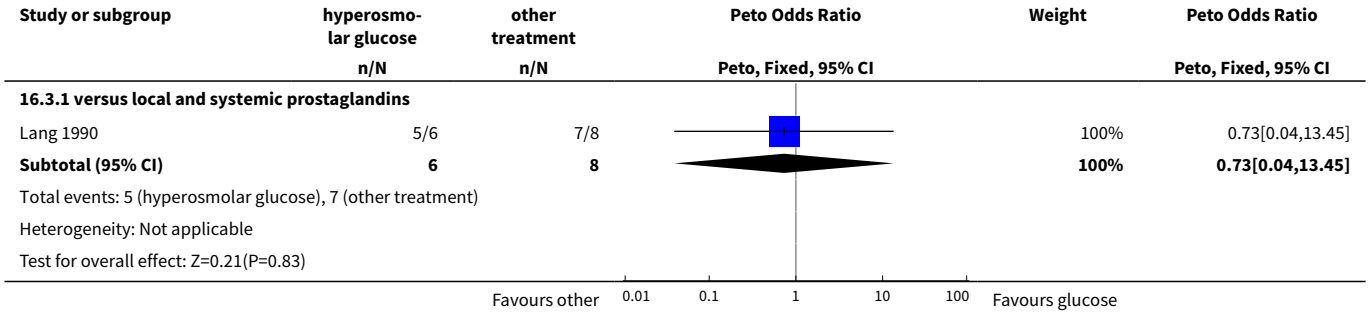
Analysis 16.1. Comparison 16 hyperosmolar glucose under laparoscopic guidance versus other treatments, Outcome 1 primary treatment success.



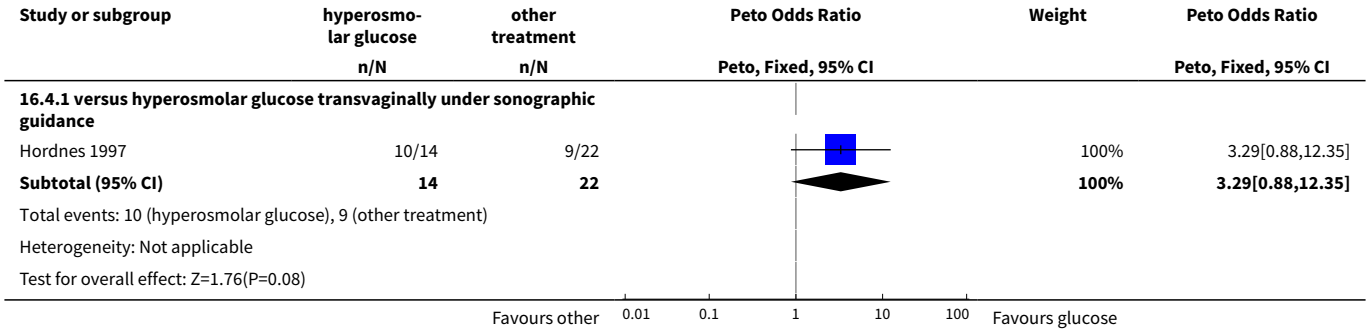
Analysis 16.2. Comparison 16 hyperosmolar glucose under laparoscopic guidance versus other treatments, Outcome 2 persistent trofoblast.



Analysis 16.3. Comparison 16 hyperosmolar glucose under laparoscopic guidance versus other treatments, Outcome 3 tubal patency.

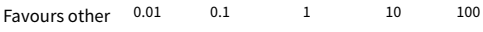


Analysis 16.4. Comparison 16 hyperosmolar glucose under laparoscopic guidance versus other treatments, Outcome 4 subsequent intra uterine pregnancy.



Analysis 16.5. Comparison 16 hyperosmolar glucose under laparoscopic guidance versus other treatments, Outcome 5 repeat ectopic pregnancy.

Study or subgroup	hyperosmolar glucose n/N	other treatment n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
16.5.1 versus hyperosmolar glucose transvaginally under sonographic guidance					
Hordnes 1997	3/14	3/22		100%	1.73[0.29,10.16]
Subtotal (95% CI)	**14**	**22**		**100%**	**1.73[0.29,10.16]**
Total events: 3 (hyperosmolar glucose), 3 (other treatment)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.6(P=0.55)					

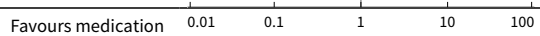


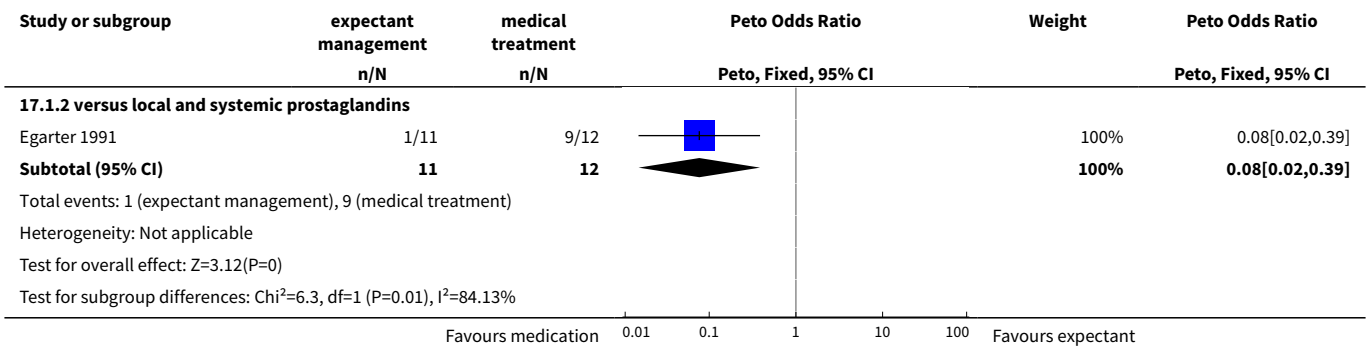
Comparison 17. expectant management versus medical treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 primary treatment success	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 versus oral MTX	1	60	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.0 [0.31, 3.28]
1.2 versus local and systemic prostaglandins	1	23	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.08 [0.02, 0.39]
2 tubal preservation	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.1 versus local and systemic prostaglandins	1	23	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.08 [0.02, 0.39]

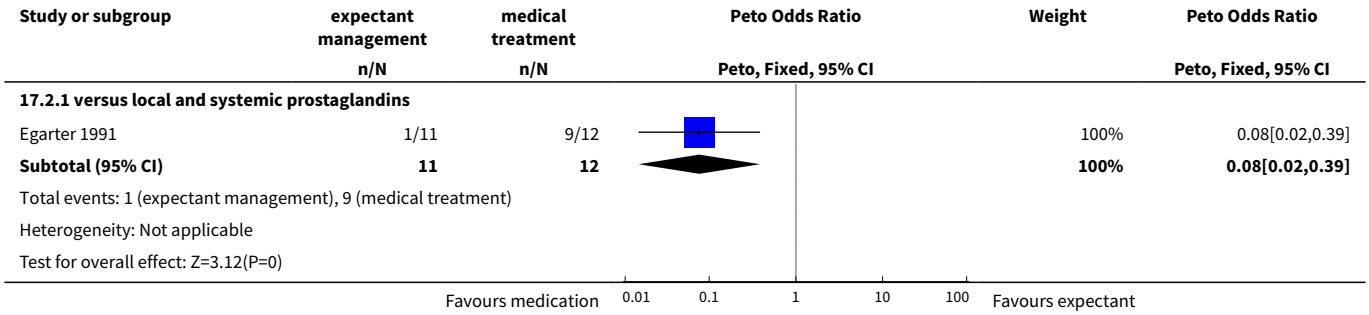
Analysis 17.1. Comparison 17 expectant management versus medical treatment, Outcome 1 primary treatment success.

Study or subgroup	expectant management n/N	medical treatment n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
17.1.1 versus oral MTX					
Korhonen 1996	23/30	23/30		100%	1[0.31,3.28]
Subtotal (95% CI)	**30**	**30**		**100%**	**1[0.31,3.28]**
Total events: 23 (expectant management), 23 (medical treatment)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					





Analysis 17.2. Comparison 17 expectant management versus medical treatment, Outcome 2 tubal preservation.



ADDITIONAL TABLES

Table 1. Risk of bias of the included studies

Study ID	Randomisation method	Allocation concealed	Blinding	no of patients	drop outs	lost to follow up
Alleyassin 2006	computer generated random number tables	adequate with sealed envelopes	no	108	0	0
Cohen 1996	computer generated random number tables	adequate	NA	20	0	0
Dias Pereira 1999	computer program	adequate	NA	140	40	10
Egarter 1991	unclear	unclear	NA	23	0	0
El-Sherbiny 2003	by computer	unclear	NA	55	0	0
Elmoghazy 2000	unclear	unclear	no	47	0	0

Table 1. Risk of bias of the included studies *(Continued)*

Fedele 1998	computer generated list	adequate by telephone	no	25	0	0
Fernandez 1991	random number table	unclear	NA	21	0	0
Fernandez 1994	blinded computer generated random number tables	adequate	NA	48	0	0
Fernandez 1995	random number table	unclear	NA	40	0	0
Fernandez 1998	random number table	unclear	NA	100	0	18
Fujishita 1995b	unclear	unclear	no	26	0	0
Fujishita 2004	computer generated randomization list	unclear	no	75	0	9
Gazvani 1998	computer generated randomization sequence	adequate with consecutively numbered enveloppes	no	50	0	0
Gjelland 1995	unclear	unclear	NA	80	0	0
Graczykowski 1997	drawing cards	inadequate	no	129	0	13
Gray 1995	unclear	unclear although sealed envelopes	NA	105		
Hajenius 1997	computer program	adequate	NA	140	40	0
Hordnes 1997	unclear	unclear	NA	80	0	0
Klauser 2005	unclear	unclear	no	51	0	0
Korhonen 1996	table of random numbers	adequate via hospital pharmacy	yes	60	0	0
Landstrom 1998	unclear	unclear	NA	31	0	0
Lang 1990	by computer	unclear	NA	31	0	0
Lundorff 1991a	unclear	unclear although sealed envelopes	NA	109	4	0
Lundorff 1991b	unclear	unclear although	NA	109	36	0

Table 1. Risk of bias of the included studies *(Continued)*

		sealed envelopes				
Lundorff 1992	unclear	unclear although sealed envelopes	NA	109	21	1
Mol 1999a	computer program	adequate	NA	140	40	0
Mottla 1992	random table	unclear	NA	21	9	0
Nieuwkerk 1998a	computer program	adequate	NA	140	51	5
Rozenberg 2003	computer generated list	adequate with sealed opaque envelopes stored in the pharmacy	yes	212	0	2
Sadan 2001	unclear	unclear	yes	20	0	0
Saraj 1998	unclear	unclear although sealed envelopes	NA	75	1	0
Sharma 2003	computer generated numbers	unclear	NA	60	0	0
Shulman 1992	unclear	unclear	no	15	0	0
Sowter 2001a	computer program	adequate with sequentially numbered opaque evelopes sealed by a third party	NA	62	0	7
Sowter 2001b	computer program	adequate with sequentially numbered opaque evelopes sealed by a third party	NA	62	0	0
Tulandi 1991a	unclear	unclear	no	34	0	16
Tzafettas 1994	unclear	unclear	NA	36	0	0

Table 1. Risk of bias of the included studies *(Continued)*

Ugur 1996	unclear	unclear	no	40	0	0
Vermesh 1989	coded card	adequate with sequential selection of umarked opaque envelope	NA	60	0	0
Vermesh 1992	coded card	adequate with sequential selection of umarked opaque envelope	NA	60	0	15
Wang 1998	unclear	unclear	no	78	0	0
Yalcinkaya 1996	unclear	unclear	yes	41	0	1
Yalcinkaya 2000	unclear	adequate with sealed envelopes at the central pharmacy	yes	100	0	44
Zilber 1996	unclear	unclear	NA	48	0	0

APPENDICES

Appendix 1. Search strings

MEDLINE (1966 to February 2006)

1 exp pregnancy, ectopic/ or exp pregnancy, tubal/ (8625)
2 ectopic pregnanc$.mp. (4960)
3 tubal pregnanc$.mp. (1325)
4 (pregnanc$ adj3 Fallopian$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (66)
5 (pregnanc$ adj3 tube$).mp. (426)
6 or/1-5 (10124)
7 randomized controlled trial.pt. (211387)
8 controlled clinical trial.pt. (70364)
9 Randomized controlled trials/ (40810)
10 random allocation/ (54389)
11 double-blind method/ (84734)
12 single-blind method/ (9609)
13 or/7-12 (359456)
14 clinical trial.pt. (421236)
15 exp clinical trials/ (173449)
16 (clin$ adj25 trial$).ti,ab,sh. (112179)

17 ((singl$ or doubl$ or tripl$ or trebl$) adj25 (blind$ or mask$)).ti,ab,sh. (83350)
18 placebos/ (24399)
19 placebo$.ti,ab,sh. (104874)
20 random$.ti,ab,sh. (437373)
21 Research design/ (42676)
22 or/14-21 (781830)
23 animal/ not (human/ and animal/) (2928551)
24 13 or 22 (786120)
25 24 not 23 (721337)
26 6 and 25 (417)
27 26 not review.ti. (403)
28 27 not review.ab. (378)
29 28 not retrospect$.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (353)
30 from 29 keep 1-200 (200)
31 from 29 keep 201-353 (153)
32 from 30 keep 1-200 (200)

EMBASE 1980 to February 2006

1 exp ectopic pregnancy/ or exp uterine tube pregnancy/ (6303)
2 ectopic pregnanc$.ab. (3588)
3 tubal pregnanc$.ab. (799)
4 (pregnanc$ adj4 tub$).ab. (2131)
5 or/1-4 (7847)
6 Controlled study/ or randomized controlled trial/ (2112948)
7 double blind procedure/ (58676)
8 single blind procedure/ (5735)
9 crossover procedure/ (17115)
10 drug comparison/ (81248)
11 placebo/ (84044)
12 random$.ti,ab,hw,tn,mf. (324740)
13 latin square.ti,ab,hw,tn,mf. (997)
14 crossover.ti,ab,hw,tn,mf. (30078)
15 cross-over.ti,ab,hw,tn,mf. (10615)
16 placebo$.ti,ab,hw,tn,mf. (130286)
17 ((doubl$ or singl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).ti,ab,hw,tn,mf. (98755)
18 (comparative adj5 trial$).ti,ab,hw,tn,mf. (5252)
19 (clinical adj5 trial$).ti,ab,hw,tn,mf. (424186)
20 or/6-19 (2549444)
21 nonhuman/ (2672524)
22 animal/ not (human/ and animal/) (12800)
23 or/21-22 (2676117)
24 20 not 23 (1488861)
25 5 and 24 (1353)
26 25 and trial.mp. (457)
27 26 not review$.ti,ab. (386)
28 27 not retrospect$.tw. (369)
29 from 28 keep 1-200 (200)
30 from 28 keep 201-369 (169)
31 from 29 keep 1-200 (200)

CINAHL - Cumulative Index to Nursing , Allied Health Literature 1982 to April Week 2 2006

1 ectopic pregnancy.mp. or exp Pregnancy, Ectopic/ (464)
2 tubal pregnanc$.ti,ab. (17)
3 (pregnanc$ adj3 tube$).ti,ab. (34)
4 (pregnanc$ adj3 Fallopian).ti,ab. (1)
5 or/1-4 (498)
6 Controlled study/ or randomized controlled trial/ (27455)
7 (drug$ adj5 compar$).ti,ab,hw,tn,mf. (1948)
8 placebo/ (3068)
9 random$.ti,ab,hw,tn,mf. (48102)
10 latin square.ti,ab,hw,tn,mf. (78)

11 crossover.ti,ab,hw,tn,mf. (3322)
12 cross-over.ti,ab,hw,tn,mf. (12095)
13 placebo$.ti,ab,hw,tn,mf. (8488)
14 ((doubl$ or singl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).ti,ab,hw,tn,mf. (10562)
15 (comparative adj5 trial$).ti,ab,hw,tn,mf. (2078)
16 (clinical adj5 trial$).ti,ab,hw,tn,mf. (32500)
17 or/6-16 (80740)
18 animal/ not (human/ and animal/) (608)
19 17 not 18 (80704)
20 5 and 19 (18)
21 from 20 keep 1-18 (18)

FEEDBACK

Interventions for tubal ectopic pregnancy

Summary

ABSTRACT
Excessively long. Text could be converted to numbers. Re-write to conform to new structure.

TYPES OF STUDIES
Inclusion of unpublished studies not as per protocol.

TYPES OF INTERVENTION
Unclear format of this section.

METHODOLOGICAL QUALITIES OF INCLUDED STUDIES
Omit mention of Koninckx 1991.
Highlight rate of exclusions after randomisation in medical treatment.

SURGICAL TREATMENT
move case-control study to Discussion section
Under comparison 7, the result for tubal preservation is quoted as "RR 1.0, 95%CI 1.0, 1.0". This confidence interval must be wrong.

DISCUSSION AND IMPLICATIONS FOR RESEARCH
Conflicting messages on laparoscopic surgery.

CONCLUSIONS-IMPLICATIONS FOR PRACTICE
Balance of emphasis on surgery vs MTX.

IMPLICATIONS FOR RESEARCH
Long discussion obscures the clear messages about future research.

EXCLUDED STUDIES
Reconsider grounds for excluding info on Lund 1955, or at least commenting on the study. Gentofte spelling.

CONFLICT OF INTEREST: None.

Reply

The review has been updated.

Contributors

Phil Alderson, April 1999

WHAT'S NEW

Date	Event	Description
11 November 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 3, 1996
Review first published: Issue 1, 1999

Date	Event	Description
16 November 2006	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Petra Hajenius: Took the lead in writing the protocol and review, performed initial searches of databases for trials, was involved in selecting trials for inclusion, performed independent data extraction and quality assessment of the included trials, was responsible for statistical analysis and interpretation of the data and was responsible for updating the review.
Femke Mol: performed searches of databases for trials since 2004, was involved in selecting new trials for inclusion for the updated review, performed independent data extraction, and commented on the draft of the updated review.
Ben Willem Mol: Performed independent data extraction and quality assessment of the included trials, was responsible for statistical analysis and interpretation of the data and commented on the drafts of the protocol and review.
Patrick Bossuyt: Commented on drafts of the protocol and review and added epidemiological and statistical expertise to the review.
Pim Ankum: Commented on drafts of the protocol and review and added clinical expertise to the review.
Fulco van der Veen: Initiated and conceptualized the review, performed searches of abstracts of both ESHRE and ASRM meetings, commented on drafts of the protocol and review and added clinical expertise to the review.

DECLARATIONS OF INTEREST

The reviewers were investigators on the randomised controlled trial comparing systemic methotrexate in a multiple dose regimen versus laparoscopic salpingostomy (Hajenius 1997), which was funded by a grant from the Health Insurance Funds Council, Amstelveen, The Netherlands (OG 93/007) from 1993 to 1996.

Prof F van der Veen is a member of the Dutch Society against Quackery. He regrets to include studies with complementary alternative medicines.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Clinical Fellow grant (no:907-00-154) from ZonMw, The Netherlands, Organisation for Health Research and Development, The Hague, Netherlands.

INDEX TERMS

Medical Subject Headings (MeSH)

Abortifacient Agents, Nonsteroidal; Methotrexate; Pregnancy, Tubal [*therapy]; Randomized Controlled Trials as Topic; Salpingostomy

MeSH check words

Female; Humans; Pregnancy